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A METHOD FOR RECORDING SPATIAL VECTORCARDIOGRAMS

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THE CONCEPT of spatial vectorcardiography originated in 1920 when Mann first constructed a monocardiogram from the three Einthoven leads. It was soon recognized that since the heart was a three-dimensional organ, the electromotive forces passing over the heart muscle must be three dimensional in character. Since each cardiac event was preceded by a period of no electrical activity and was terminated by a period of no electrical activity, such forces must inscribe a spatial loop. This loop is representative of the pathway and magnitude of the electrical events of the heart. The ordinary electrocardiogram is merely the graphic representation of a portion of the electromotive forces inscribed by the loop; each electrocardiographic lead may be called a part, whereas the spatial loop is the whole of an electrical event.

The major problem concerned with three-dimensional forces was in finding a method of measuring them. It was necessary to find three electrocardiographic leads that could be utilized to measure the three components of the force, namely, projection of the force from side to side, up and down, and forward and backward. Three such leads would constitute a reference system for spatial vectorcardiography. As yet no standard reference system has been accepted or established.

It seems important to establish a convenient method of recording vectorcardiograms which are true representations of the electrical events as they occur in the heart. The present study was undertaken to find a reference system of three bipolar leads that most satisfactorily accomplished this end. The reference system chosen for evaluation was then used in 100 cases and compared to records obtained by the cube system as it is now employed by Grisham[2] and others.

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To use bipolar leads interchangeably in forming vectorcardiograms, the leads must be equal, one to the other. That is, a force of one millivolt in an anterior-posterior lead must produce a deflection of the same amplitude as a millivolt in a right-left direction does in a right-left lead. If the leads are not comparable, standardizing factors must be introduced. For leads to be comparable to one another they must meet two requirements: (1) their electrodes must be equidistant from the heart (remote), and (2) the angle to the force subtended by the electrodes which they measure must be equal.

Grant[3] has indicated that any electrode over 10 to 12 cm. distance from the heart in the human subject may be considered equidistant or remote. Assuming the correctness of Grant's statement, all points for a satisfactory reference system must be 12 cm. from the heart.

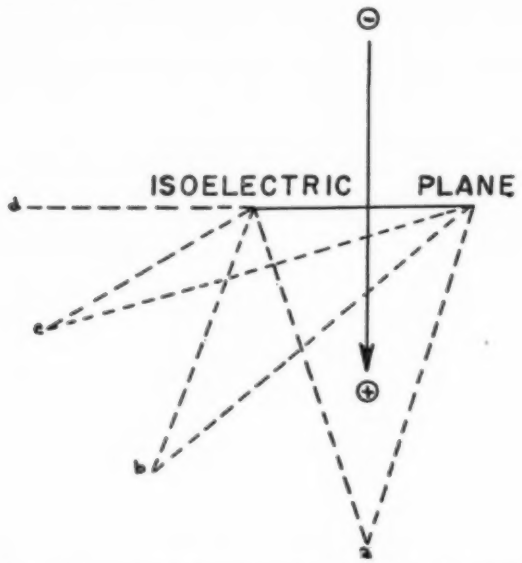

Fig. 1.—Electrode position (*a*) records the maximum potential of the forces, while position *d* is 90 degrees from the force recording no potential.

The work of Gauss in measuring the potential of a double layer was applied by Bayley[4] to the heart. Wilson[5] introduced the term "solid angle" to measure the potential manifest at any point distant to the double layer. Simply stated, one may assume that when an electrode is parallel to a force resulting from destruction of a double layer, maximum potential is received from that force; when an electrode is at right angles to a force, the result of the force is zero. The angle subtended by the electrode, relative to the force, measures the total force, a fraction of it, or none of it, within an arc of 90 degrees (Fig. 1).

The importance of the angle subtended by the electrodes of a bipolar lead relative to a force being measured is illustrated again in Fig. 2. In Lead AB the potential difference is: $10 - (-10) = 10 + 10 = 20$ whereas for Lead A′B′ potential difference is: $5 - (-5) = 5 + 5 = 10$. In each instance the electrodes are equidistant from the force measured but the angle subtended by the electrodes is quite different. Therefore, the angle subtended by the electrodes of the

three leads must be comparable in order to use these leads interchangeably for spatial orientation.

It is recognized that any spatial reference system will have certain faults. Perhaps the body cannot always be considered as a homogenous volume conductor or the character of the conducting tissues may make minor differences in some instances. It was hoped with the present study to find a bipolar reference system of three leads that most nearly satisfied the two criteria outlined above and was as simple as possible. To accomplish this goal, three leads were selected, a frontal lead consisting of right-arm negative, left-arm positive (Einthoven's Lead I), a sagittal lead with a negative electrode on the right arm and a positive electrode in the right midaxillary line at the level of the second lumbar vertebra, and a horizontal lead consisting of a positive electrode in the midline over the second lumbar vertebra with the negative electrode just above the umbilicus.

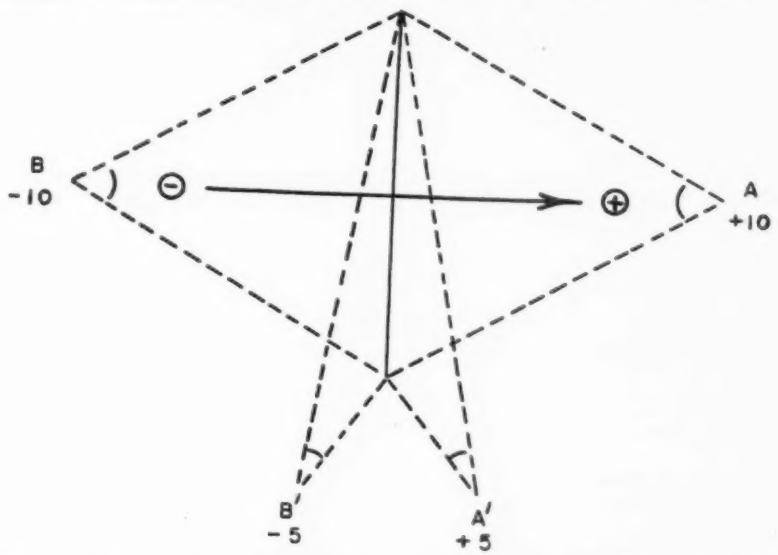

Fig. 2.—Difference in potential received from the same force by bipolar Lead AB and bipolar Lead A'B'.

The right arm and left arm electrodes are sufficiently far enough removed from the heart to be considered equidistant. In the average-sized adult the mid right axillary line electrode is 15 to 17 cm. distant from the heart, the abdominal electrode 15 cm. from the ziphoid process or beyond the necessary 10 to 12 cm. from the heart[3] to be considered remote. The second lumbar vertebra is farther from the heart than the commonly used seventh dorsal vertebra of the tetrahedron system[5] and can be considered remote. At these distances all five electrode positions can be considered remote or equidistant from the heart.[3] The angle subtended by the five electrodes relative to the force measured in each lead is the maximum the body will conveniently accommodate and still satisfy the criteria necessary for remoteness.

METHOD OF RECORDING VECTORCARDIOGRAMS

The electrodes were placed on the subject in the manner described above. The patient cable was connected to two channels of a multiple-lead direct writer.*

*Sanborn Poly-Viso, Sanborn Company, Cambridge, Mass.

The impulse passed from the patient to the electrocardiographic amplifiers directly to an oscilloscope* utilizing channel X and Y to record the vectorcardiogram. The cathode-ray beam was interrupted every 1/360 second (0.0028 second) utilizing a square wave generator.† Simultaneous electrocardiograms of the two leads used to make any vectorcardiogram could be recorded. The Y axis of the oscillograph was reversed in such a manner that a positive force produced a downward displacement of the cathode-ray beam.

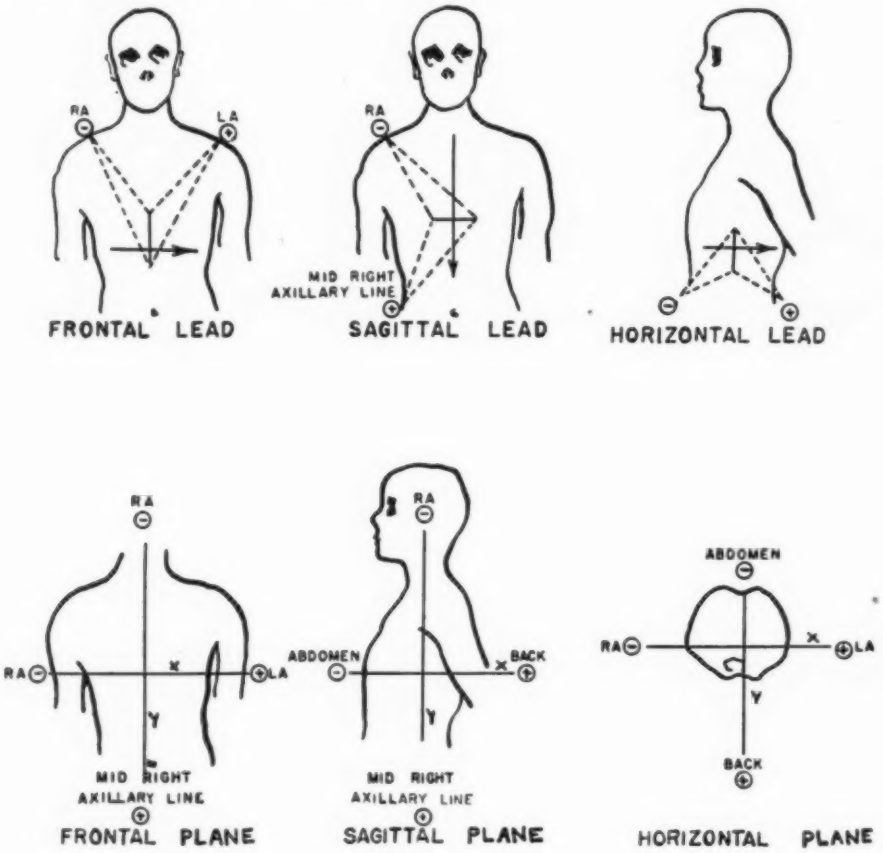

Fig. 3.—Electrode placement for each lead of the spatial reference system and the leads that comprise each plane for recording the vectorcardiogram.

The frontal plane was recorded by use of the frontal lead (Lead I) for the X axis and the sagittal lead for the Y axis. The frontal plane vectorcardiogram then appears on the screen as if one were facing the patient. The record obtained on the oscillograph screen is then photographed with a 35 mm. camera.

The horizontal plane was recorded by use of the horizontal lead for the Y axis and the frontal lead (Lead I) as the X axis. This gives a horizontal view of the loop as it would appear if one were looking toward the base of the heart from below the apex. This method of viewing is the same as that used in referring to clockwise and counterclockwise rotation of the heart.

*Dumont Cathode Ray Oscillograph 279.
†Dumont Square Wave Generator, Type 185-A.

The sagittal plane was recorded by use of the sagittal lead for the Y axis and the horizontal lead for the X axis. The sagittal plane of the loop appears on the screen as if one were looking laterally through the chest from left to right (Fig. 3.)

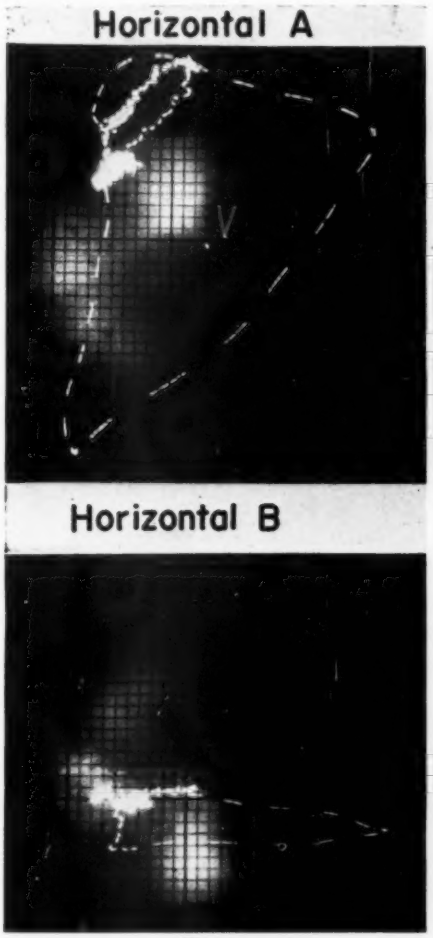

Fig. 4.

Fig. 5.

Fig. 4.—*Horizontal A* using the modification.
Horizontal B using the usual cube reference system in the same subject.
Fig. 5.—*Sagittal A* using the modification.
Sagittal B using the casual cube reference system in the same subject.

MATERIAL

One hundred subjects who had no evidence of heart disease clinically, radiographically, or by routine electrocardiography were selected. A vectorcardiogram in the frontal, horizontal, and sagittal plane was recorded in each instance. The electrocardiogram produced by each lead comprising the vectorcardiogram, six limb leads, and six V leads were recorded.

The major difference in the loops obtained and the method used by Grishman and others[2] was the difference in the horizontal (anterior-posterior) leads. Since both systems satisfy the requirement of remoteness this difference in loop form

must be due to the angle subtended by the electrodes relative to the horizontal force. The electrodes of the rectangular cube system[2] use the anterior and posterior right axillary lines. One can compare the two reference systems by referring to Fig. 2: Lead AB representing our modification and A′B′ representing the rectangular cube. Figs. 4 and 5 illustrate the differences in the vectorcardiograms using the two techniques. The negatives have been reversed when necessary to make comparison easier.

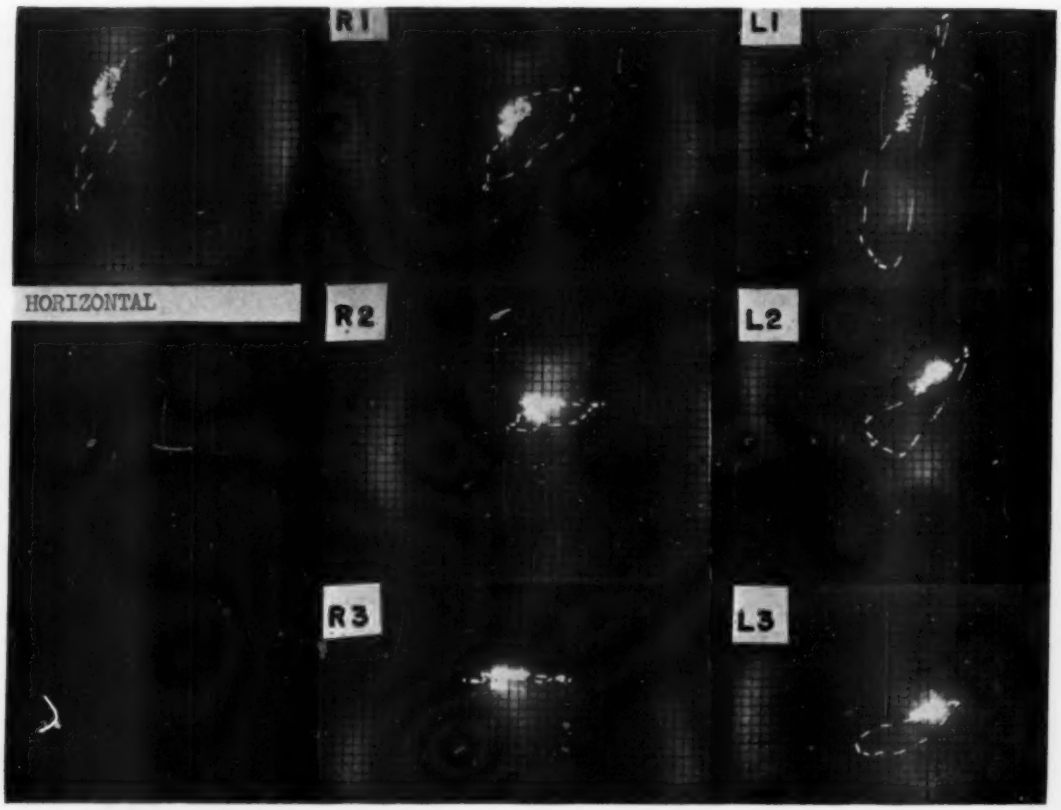

Fig. 6.—Effect of changing the angle subtended to electromotive force by changing the position of the electrodes as follows:

X axis, Lead I (frontal lead).
Y axis, Horizontal lead (abdomen and back).
R_1, Midclavicular and midscapular line on the right.
R_2, Anterior axillary and posterior axillary right side.
R_3, Each electrode 1 inch apart.
L_1, Midclavicular and midscapular line on the left. L_1 illustrates loss of remoteness of electrode.
L_2, Anterior axillary and posterior axillary line on the left.
L_3, Each electrode 1 inch apart.

To determine what differences one might expect by changing the position of the electrodes of the horizontal lead (anterior-posterior), our modification[6] was used and the horizontal lead was moved progressively to the right and progressively to the left, in the same plane. Fig. 6 illustrates the fact that there is a progressive decrease in electrical potential measured by the horizontal lead as it

is moved more laterally. In the case illustrated it will be noted that in the L_1 position (left midclavicular and left midscapular line) there is a marked increase in the magnitude of the horizontal component. This can be explained by the electrode being sufficiently close to the heart so that it is no longer remote.

The sagittal lead (right arm (−), right midaxillary line (−)) was compared to standard Leads II and III. It was found to compare favorably with an axis intermediate between 60 and 120 degrees or an axis of 90 degrees. Figs. 7 and 8 both illustrate this point. The frontal lead is identical with Einthoven's Lead I and requires no discussion.

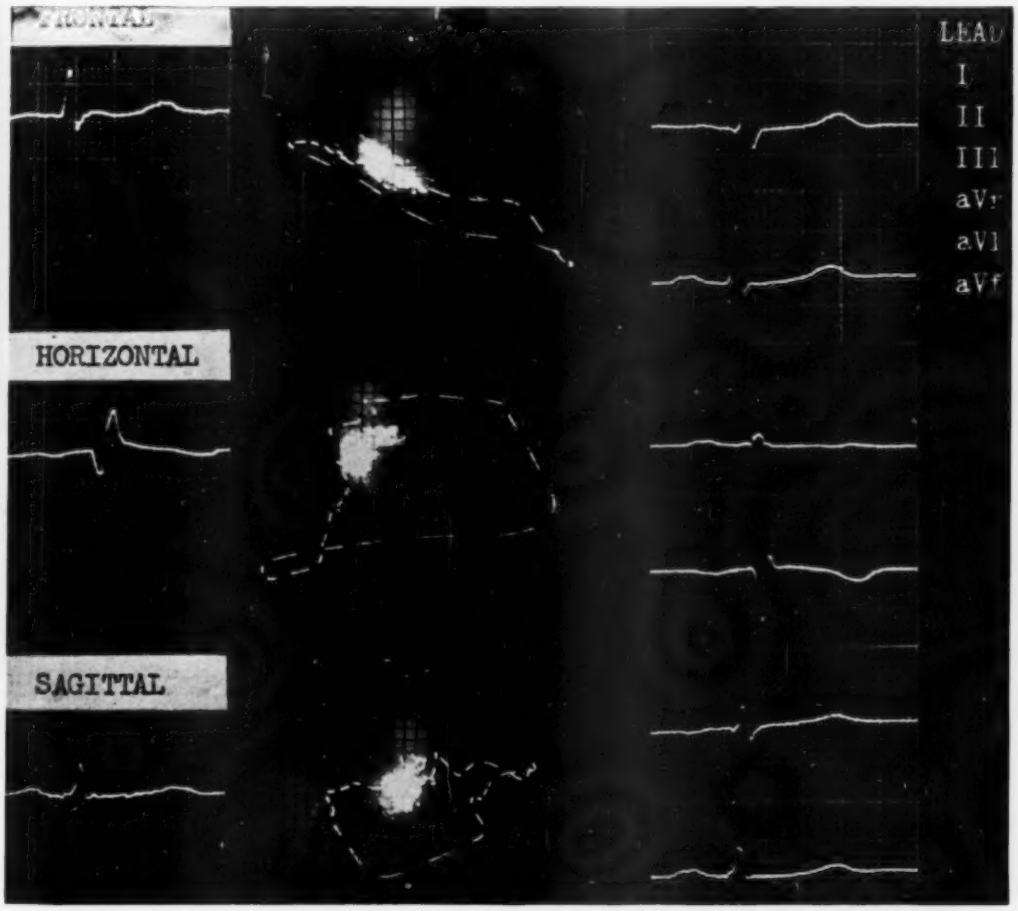

Fig. 7.—Patient 45 years of age. *Frontal*, Clockwise. *Horizontal*, Clockwise. *Sagittal*, Counterclockwise.

SUMMARY

Three perpendicular bipolar axes which constitute a spatial reference system have been described. The electrodes comprising the reference system are remote or equidistant. The angle subtended to the force measured in each instance was

as great as the body would accommodate and not violate the distance necessary for remoteness.

This reference system was compared in one hundred instances with the rectangular cube method used by Grishman and others. The chief difference in the two reference systems was found in the measurement of the anterior-posterior

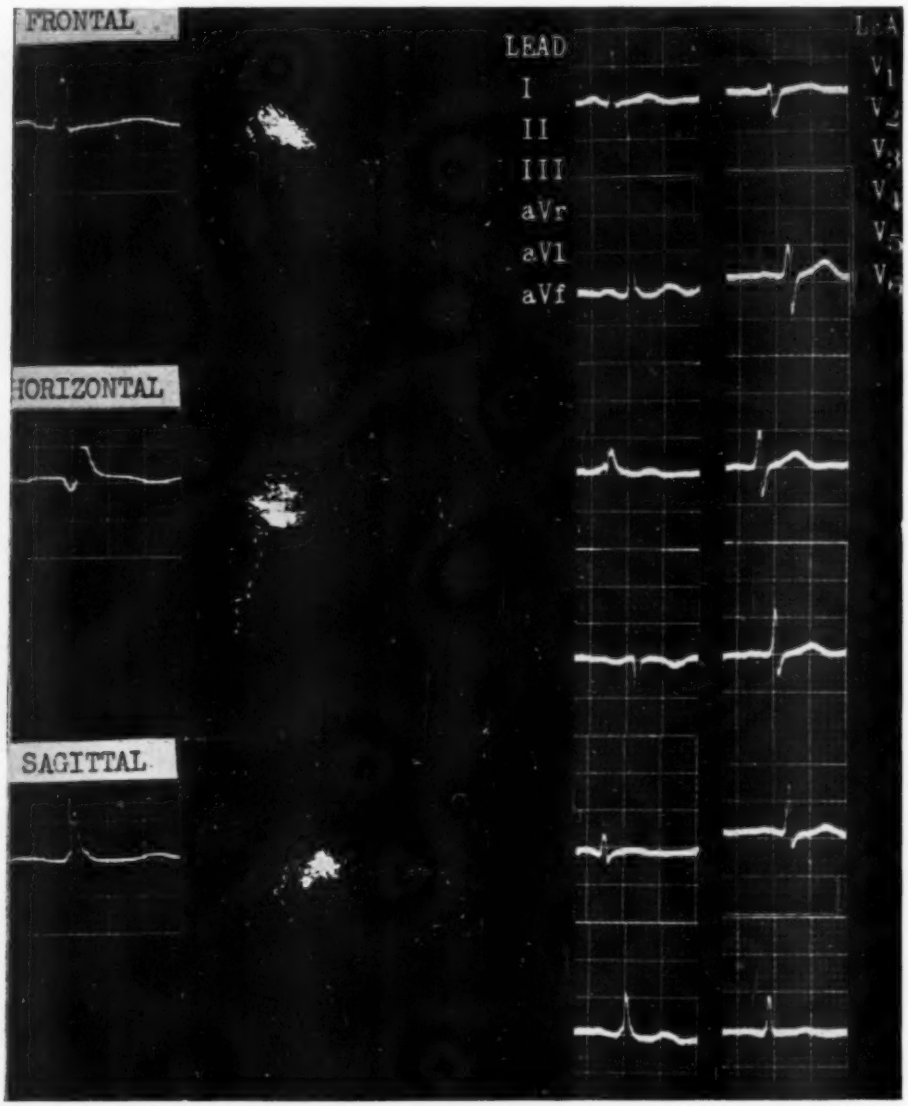

Fig. 8.—Patient 56 years of age. *Frontal*, Clockwise. *Horizontal*, Clockwise. *Sagittal*, Counterclockwise.

electromotive force. In each instance, using our modification, the anterior-posterior component was greater. We believe this change is due to the difference in the angle subtended by electrodes comprising this bipolar lead in the two

systems. It is recognized that the electrode placement of this system, as with other spatial reference systems, may not always be considered remote. However, this factor is not inherently greater in the suggested reference system than other currently employed methods. Therefore, we suggest that the method described here may more closely reflect the true potential manifested in the heart.

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THE SPATIAL VECTORCARDIOGRAM DURING THE FIRST DECADE OF LIFE

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THE PRESENT study was undertaken to determine the characteristics of the spatial vectorcardiogram during the first week of life and how it changed during the first decade.

The method used was the reference system described in our previous publications.[1,2] The three perpendicular axes forming the spatial reference system were: (1) frontal lead (right arm negative, left arm positive); (2) horizontal lead (abdomen above the umbilicus, negative, second lumbar vertebra, positive); (3) sagittal lead (right arm, negative, mid right axillary line, positive). The reference systems as they apply to the frontal, horizontal, and sagittal planes are shown in Fig. 1.

The subjects used for the survey were free of any indication of cardiac disease as revealed clinically, radiographically, and by electrocardiogram. Forty-six subjects were studied. They are divided into nine groups for analysis as shown in Table I.

TABLE I

GROUP	AGE	NO. OF SUBJECTS
I	1 to 7 days	10
II	4 to 6 weeks	4
III	4 to 5 months	2
IV	9 to 12 months	3
V	16 to 24 months	6
VI	2.5 to 4 years	5
VII	5 years	5
VIII	6 to 8 years	5
IX	9 to 10 years	6

The vectorcardiogram during the first week of life was deviated to the right in all ten cases. In two cases the major portion of the QRS sE loop was directed toward the right shoulder. Eight frontal plane QRS loops were clockwise and two counterclockwise. Fig. 2 demonstrates a typical vectorcardiogram in a

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7-day-old subject. The horizontal plane showed a QRS sE loop on the right side of the point of origin. All horizontal loops were counterclockwise. The sagittal plane was recorded in a counterclockwise manner. We have noted two important characteristics of the vectorcardiogram in the newborn infant: (1) its location to the right of the point of origin, and (2) its counterclockwise spatial direction (Fig. 2).

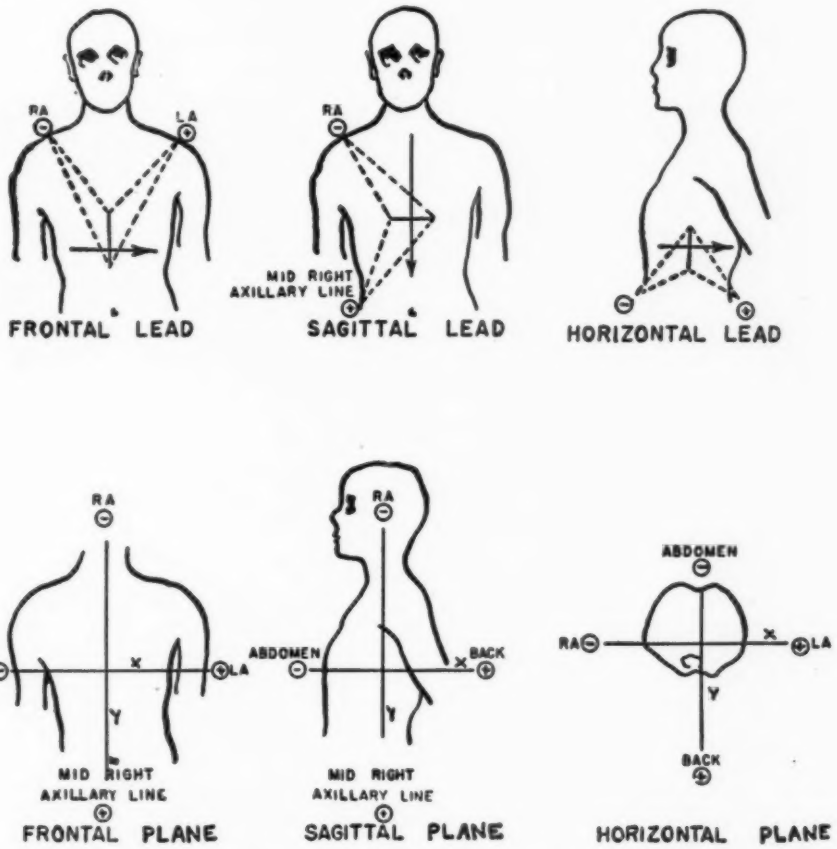

Fig. 1.—Illustration of electrode placement for the three perpendicular leads comprising the spatial reference system.

When the subject was 4 to 6 weeks of age, the vectorcardiogram assumed a more nearly vertical projection in the frontal plane (Fig. 3). The QRS sE loop was still largely to the right of the point of origin. In the horizontal plane the loop assumed its counterclockwise pathway. The initial deflection, however, was more to the left than previously noted and the entire spatial loop was shifted farther anteriorly. One of the four subjects had a figure-eight loop when viewed from the horizontal plane. As in the other records, the initial deflection was anterior and to the left.

The two subjects of 4 to 5 months of age had spatial vectorcardiograms that were vertical or deviated slightly to the left of 90 degrees. Both subjects had figure-eight horizontal projections of the spatial loop (Fig. 4).

When the subjects were from 9 to 12 months of age, another important change was found in the vectorcardiogram. In the frontal plane, three subjects had a nearly vertical projection of the loop. In the horizontal plane the loops were recorded in a clockwise fashion (Fig. 5). The QRS sE loop was largely to the left of the point of origin. Thus the spatial loop that was recorded counterclockwise and to the right in the newborn infant was at this time recorded clockwise and nearly vertical.

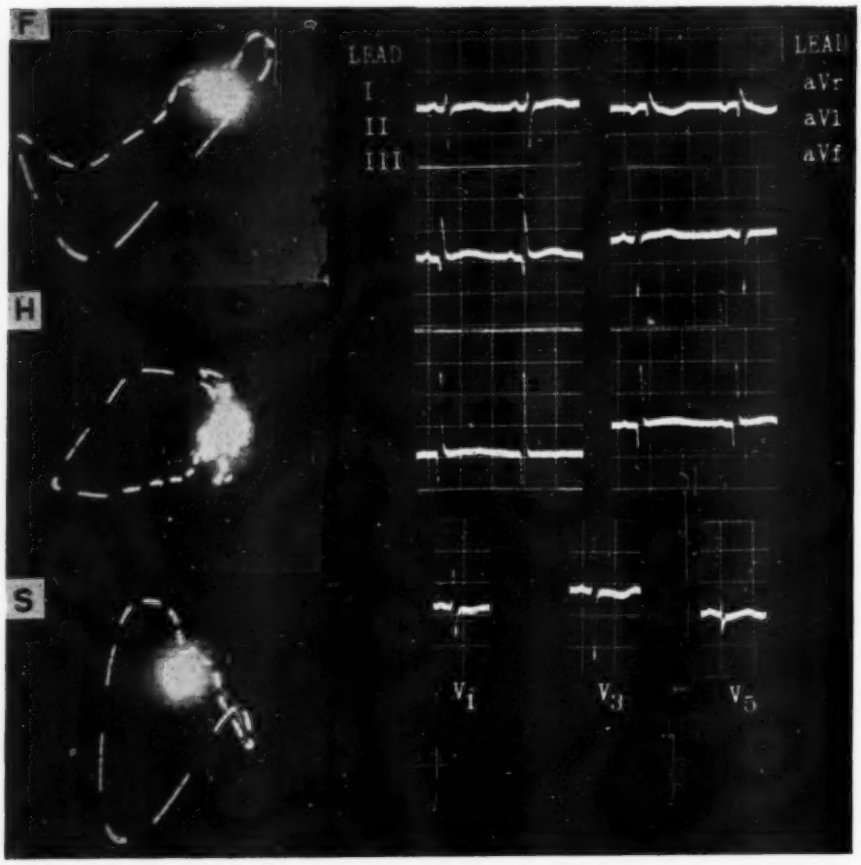

Fig. 2.—7-day-old infant. *F*, Frontal; clockwise. *H*, Horizontal; counterclockwise. *S*, Sagittal; counterclockwise.

Six subjects were chosen in the age group 16 to 24 months of age. Two subjects had spatial records not unlike those of the 4 to 6 weeks age group, with the spatial loop being recorded to the right of the point of origin and in a counterclockwise fashion. In two instances the figure-eight type of horizontal projection was observed (Fig. 6). The remaining two subjects showed the spatial loop largely to the left of the point of origin in the horizontal plane and inscribed in a clockwise manner. Five subjects were between the ages of 2.5 and 4 years.

Spatial loops were clockwise in four subjects, counterclockwise in one (Fig. 8). The initial deflection was to the left and anterior in all but one case which was to the right and anterior.

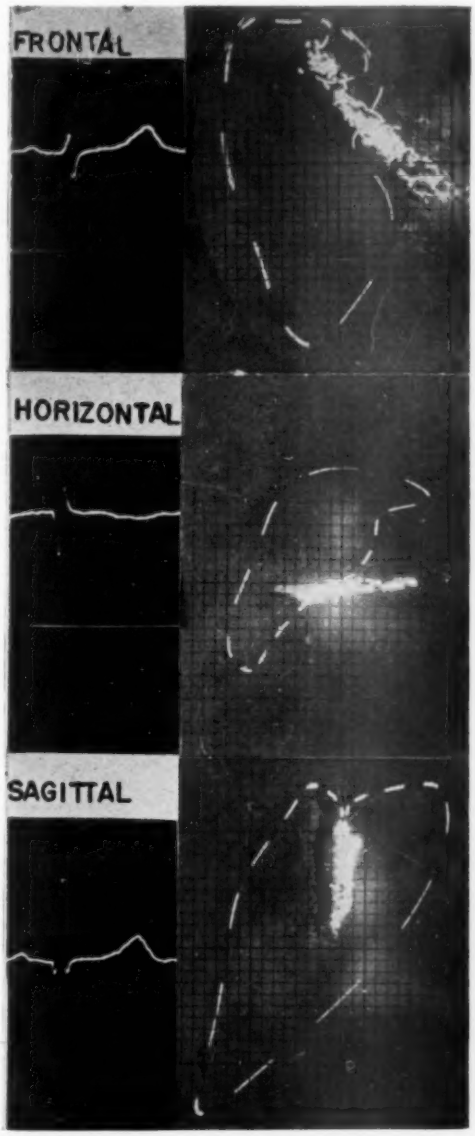

Fig. 3.—5-week-old infant. *Frontal*, Clockwise. *Horizontal*, Counterclockwise. *Sagittal*, Counterclockwise.

The 5-year-old subjects were five in number. The frontal projection of the loop was usually plus 60 to plus 70 degrees. In two instances the horizontal projection appeared as the figure-eight pattern. All others had spatial loops to the left of the point of origin and recorded in a clockwise manner (Fig. 7).

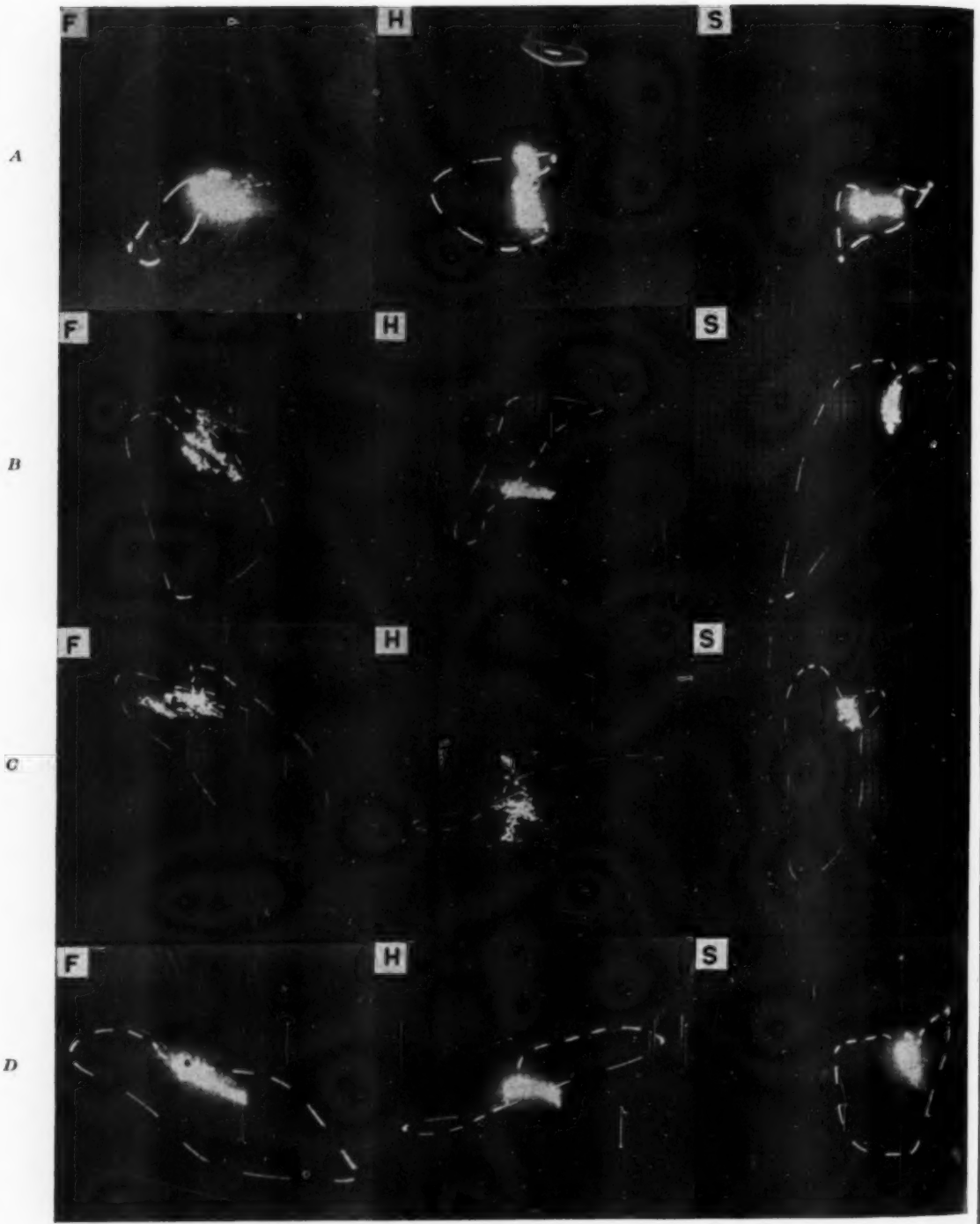

Fig. 4.—The QRS sE loop as it appears in a subject from 4 days to 9 months of age. *A*, 4 days; *B*, 6 weeks; *C*, 4½ months; *D*, 9 months.

The vectorcardiograms of eleven subjects, ages 6 to 10 years, were similar to those of the 5-year-old group.

The principal changes occurring in the spatial vectorcardiogram from birth to 10 years are illustrated in Figs. 4 and 8. These changes occur largely in the

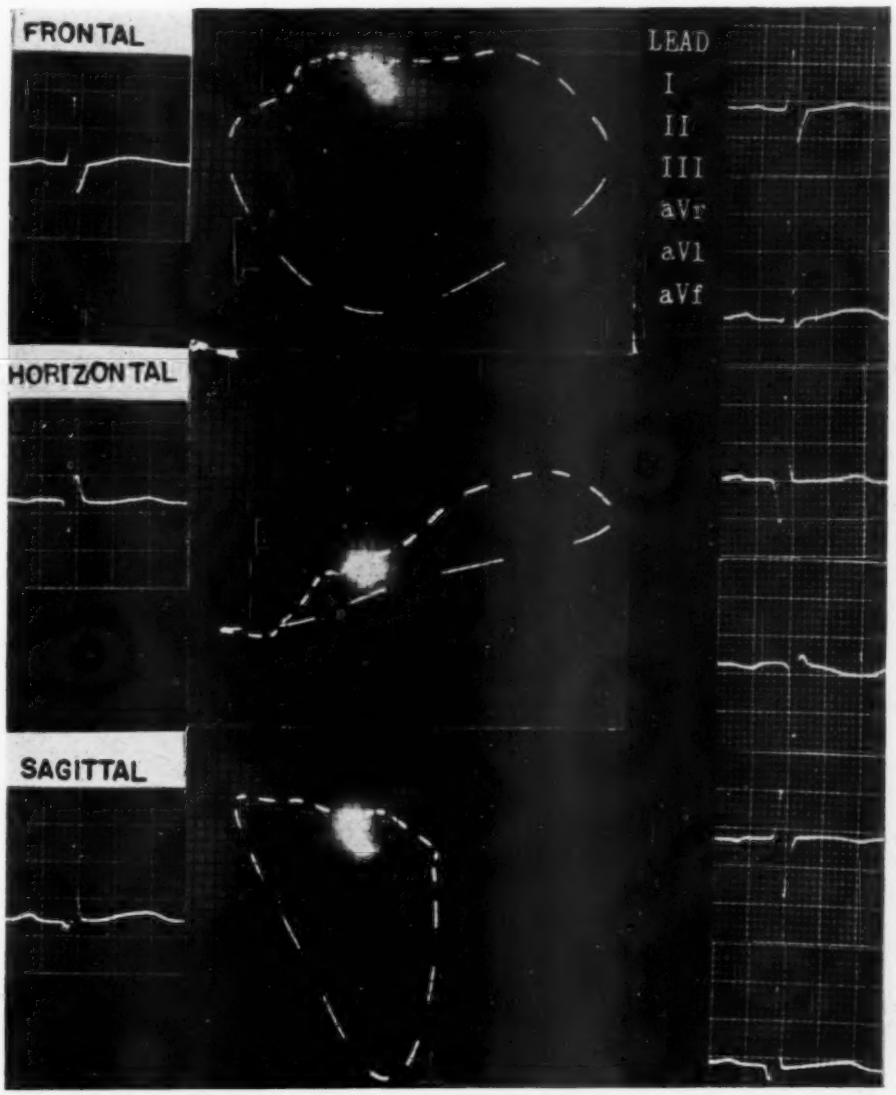

Fig. 5.—10-month-old infant. *Frontal*, Clockwise. *Horizontal*, Clockwise. *Sagittal*, Counterclockwise.

first five years of life with the greatest changes occurring in the first year. During the first week of life, ventricular depolarization describes a pathway which is to the right of the point of origin. This produces a counterclockwise pattern when projected on the horizontal plane.

It appears, therefore, that the spatial loop is rotated more anteriorly with age. A figure-eight pattern in the horizontal plane was seen in one instance as early as the age of 4 weeks. This pattern appears to be common from 4 months to 6 years of age. The spatial loop becomes oriented to the left of the point of

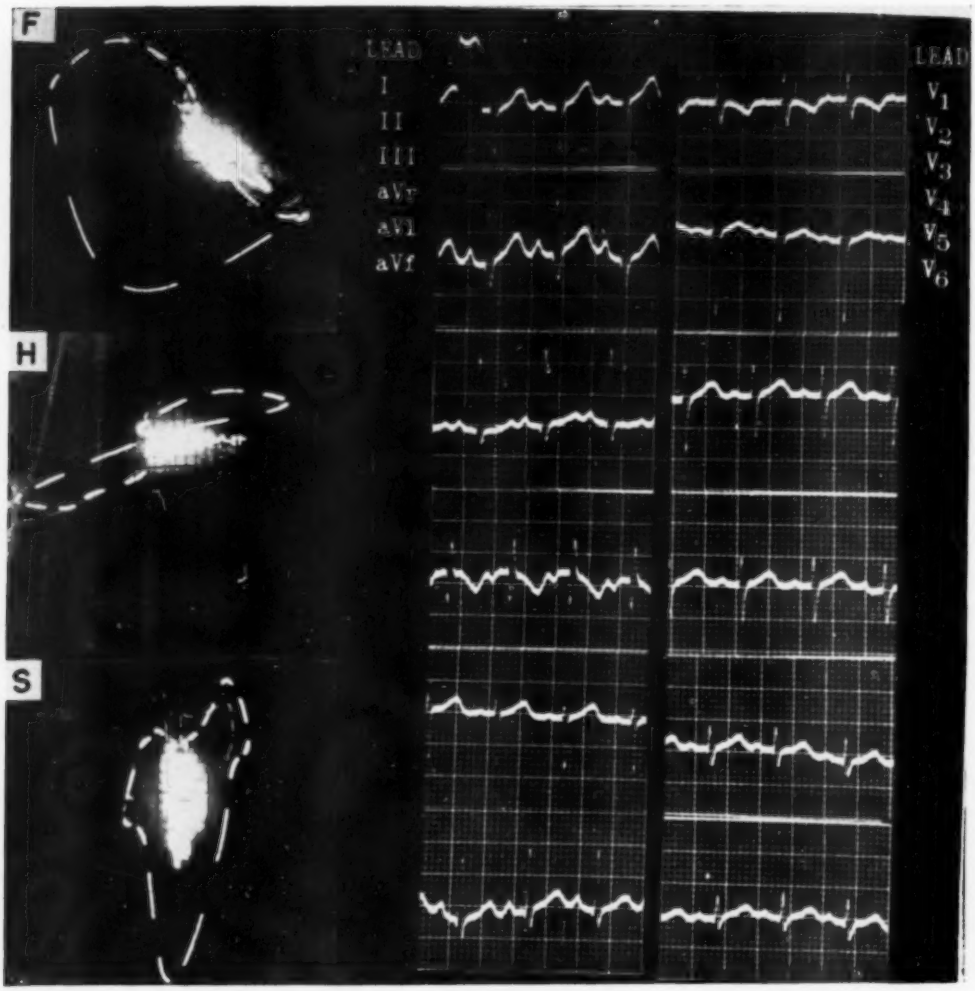

Fig. 6.—14-month-old infant. *F*, Frontal; clockwise. *H*, Horizontal; clockwise (Fig. 8). *S*, Sagittal; counterclockwise.

origin as early as 10 to 12 months of age. This results in a reversal of the direction of the horizontal loop which then becomes clockwise. The figure-eight pattern in the horizontal plane was not present at birth, and is not common in normal subjects over 20 years of age (unpublished data).

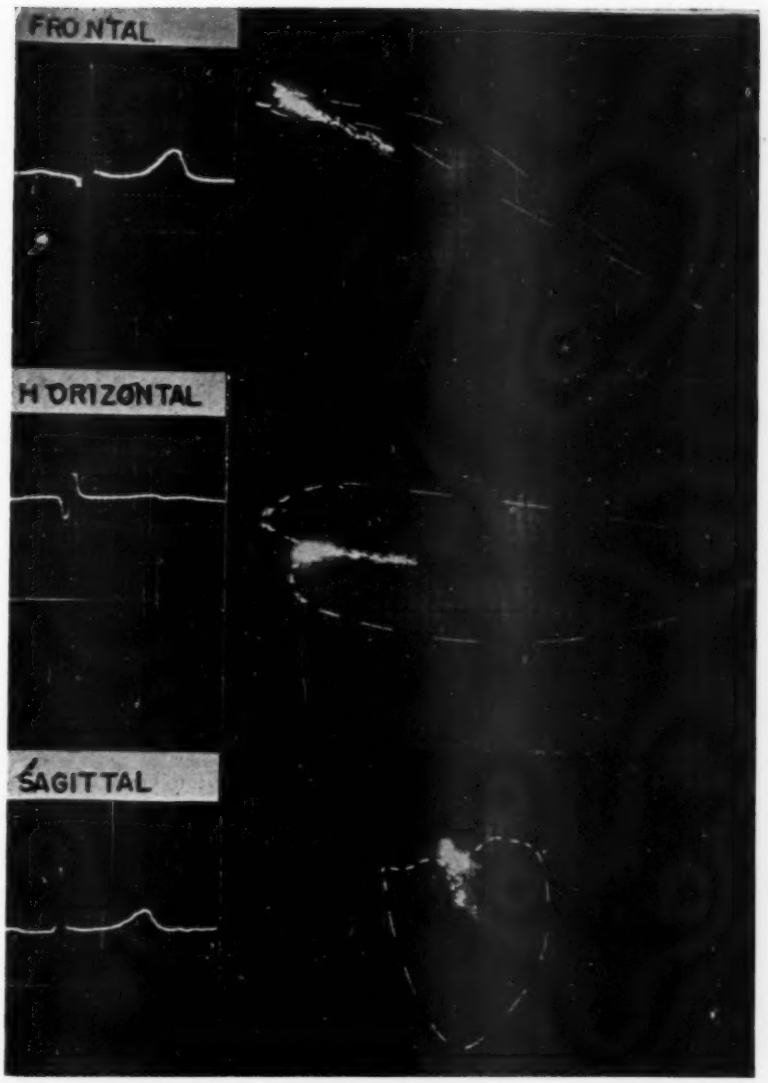

Fig. 7.—5-year-old child. *Frontal*, Clockwise. *Horizontal*, Clockwise. *Sagittal*, Counterclockwise.

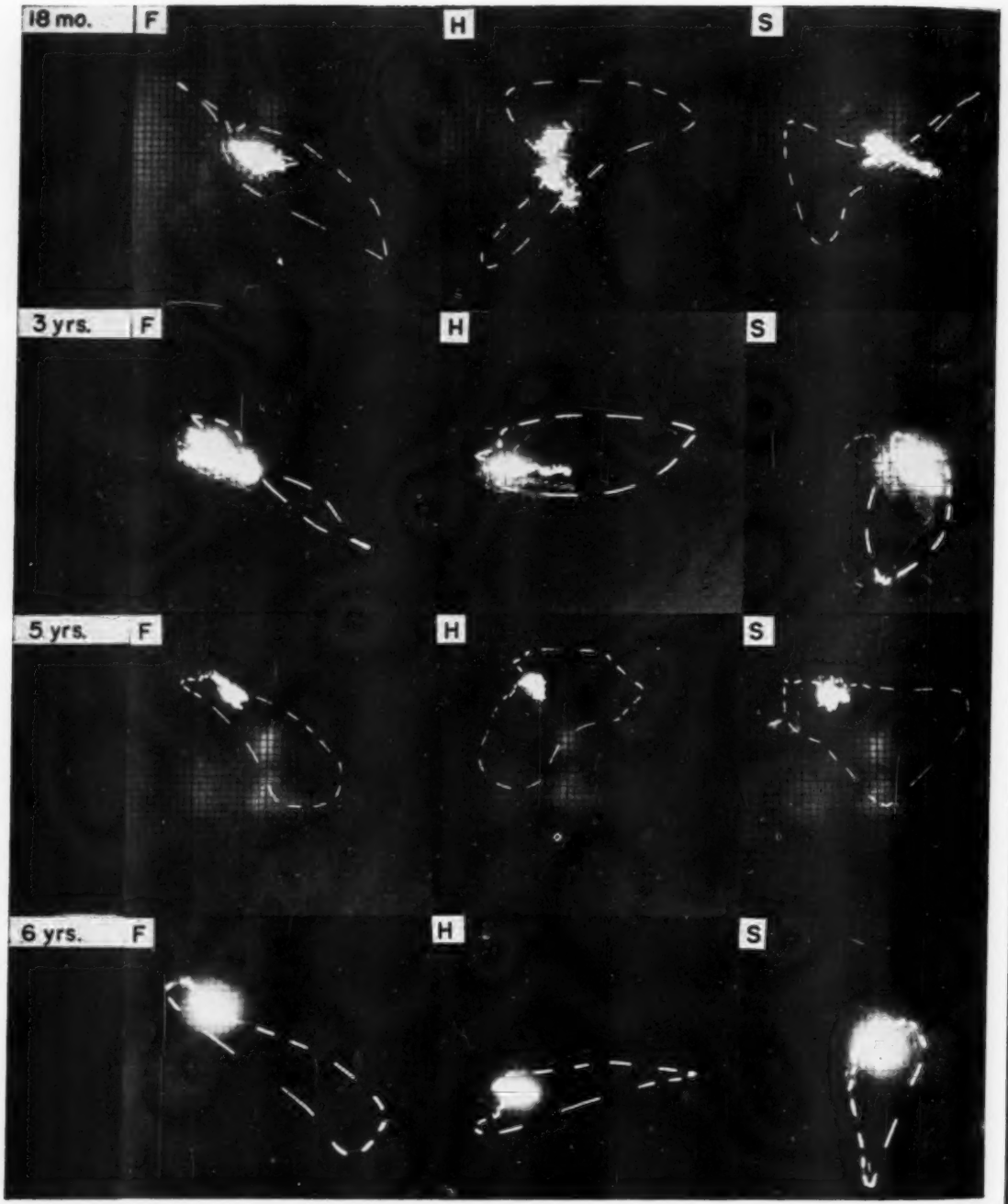

Fig. 8.—The QRS sE loop as it appears in a subject from 18 months to 6 years of age.

SUMMARY

The spatial electrocardiogram has been recorded in forty-six subjects, all in the first decade of life. Data were obtained which confirmed the report by Scherlis and associates for ages past 4 months of life.[3] However, in addition, we have recorded the spatial loops of infants, from birth to 1 week of life, and have noted: (1) the location of the loop to the right of the point of origin, and (2) the loop occurred in a counterclockwise direction. Any attempt at determining vector loops on infants raises the probability that the electrode sites are not remote. However, this fault is inherent in the size of the subject and the errors imposed must be assumed.

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LEVOCARDIA

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LEVOCARDIA is a rare congenital anomaly in which a left-sided heart occurs in the presence of situs inversus viscerum. The terminology of this condition is quite varied, and the names which have been applied to this complex include situs inversus of the abdominal viscera with levocardia, congenital heart disease with sub-diaphragmatic lateral heterotaxy, and congenital heart disease with isolated inversion of the abdominal viscera. Since all of these terms would seem to exclude a common feature of the complex, namely, transposition of the lungs, we have preferred to use the more simple and general designation levocardia, which best emphasizes the isolated nature of the left-sided orientation of the heart with respect to the rest of the viscera.

Only thirty-three cases of levocardia have been reported. These cases have been reviewed, in part, by Lichtman,[1] Forgacs,[2] Donzelot and associates,[3] Thomson,[4] and Young and Griswold.[5] The embryogenesis of levocardia is obscure. The detection of the numerous anomalies in any one case may require great ingenuity. The case to be reported was rather intensively studied by means of electrocardiography, vectorcardiography, and repeated cardiac catheterization and angiocardiography. Despite this imposing collection of the more refined techniques of modern cardiologic diagnosis, the complete array of congenital abnormalities in this patient was not uncovered until post-mortem examination was performed.

The following is the report of a case of levocardia with situs inversus of the abdominal viscera and lungs, corrected transposition of the great vessels, common ventricle, interatrial septal defects, pulmonic stenosis, and anomalous distribution of the coronary arteries.

CASE REPORT

A. G., a 30-month-old white girl was first admitted to the Pediatric Service of the Mt. Sinai Hospital in June, 1949. The child had been intensely cyanotic since birth. Clubbing of the fingers had become evident during infancy. The child had a markedly diminished exercise tolerance, never being able to run or to walk more than a short distance. Her mental development had been normal.

Physical examination revealed marked cyanosis and advanced clubbing (Fig. 1), but no dyspnea at rest. Blood pressure was 104/80 mm. Hg. The lungs were clear. Gallop rhythm

From the Cardiovascular Research Group of the Mt. Sinai Hospital, New York, N. Y.
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was audible at the cardiac apex. A moderately loud, harsh, systolic murmur was best heard over the third left intercostal space and was transmitted to the neck and toward the apex. The liver edge was just palpable beneath the left costal margin and the tip of the spleen could be felt on the right.

There was marked polycythemia with a hemoglobin of 18 grams per cent, a red cell count of 7.8 million per c.mm. and a hematrocrit of 71 per cent. The electrocardiogram (Fig. 2) showed that in the standard leads the P waves were tall, notched, and upright in Leads I and II, and inverted in Lead III. A prominent S wave was present in Lead I, while Lead II had a QS configuration. Lead III showed an equiphasic QR. The unipolar extremity leads were of interest in that the QRS complex was completely upright in aV_R and completely inverted in aV_L. The precordial leads were characterized by tall R waves over the right side of the chest, and a deep QS pattern in V_6. In every precordial lead, the P wave was upright. The interpretation of the electrocardiogram was that of right ventricular hypertrophy and of atrial hypertrophy. None of the characteristics of dextrocardia with inversion of the chambers was present. The pattern being quite unusual, a vectorcardiogram was recorded in an effort to secure further information. Another electrocardiogram was recorded prior to a spatial vectorcardiogram; it was similar in all respects to the earlier record, except that the P waves were inverted in Leads I, aV_L, and V_6.

Fig. 1.—The appearance of the patient at the time of her first admission.

The vectorcardiogram (Fig. 3) revealed that the QRS loop was oriented superiorly, to the right, and essentially anteriorly. There was no evidence of conduction delay. The P loop was large and oriented anteriorly and somewhat to the right and inferiorly. The T loop was inscribed in a direction opposite to that of the QRS loop. The direction of inscription of the QRS loop in the horizontal plane was clockwise, counterclockwise in the sagittal plane, and clockwise in the frontal plane projection. The vectorcardiogram was interpreted by Drs. Arthur Grishman and Richard Lasser as showing right ventricular hypertrophy of advanced degree. This interpretation was based on the clockwise inscription of the QRS loop, which was oriented anteriorly and superiorly. The orientation of the P loop is of special interest, since in the frontal plane it is inscribed perpendicularly to Lead I. It can easily be seen how a slight shift in the P wave vector could produce either an upright or inverted P wave in Lead I. Apparently this slight shift in the P wave vector accounted for the inverted P wave in Lead I in the second electrocardiogram.

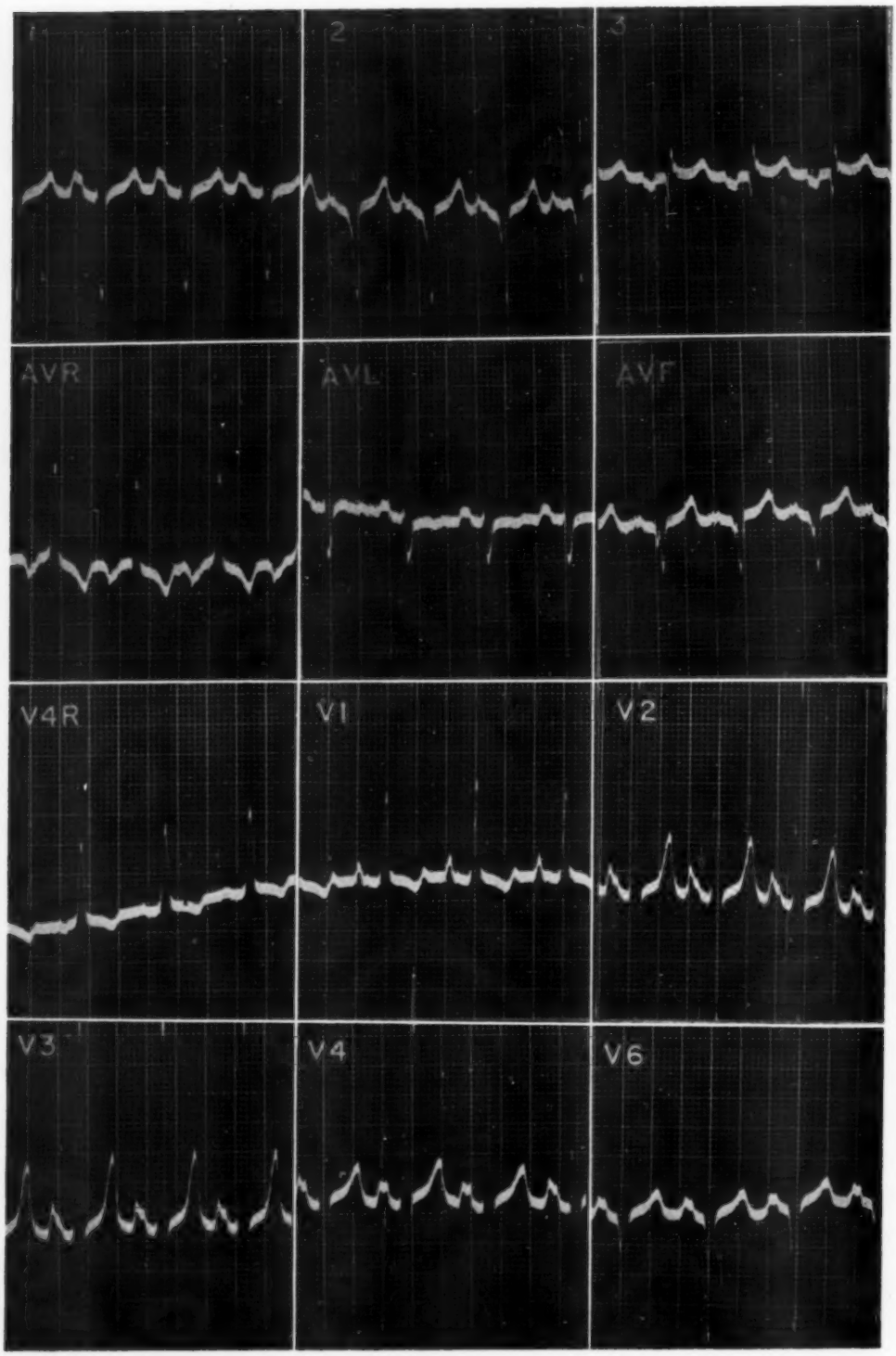

Fig. 2.—Electrocardiogram showing marked right ventricular hypertrophy pattern. The P waves are prominent, upright, and notched.

Roentgenogram of the chest (Fig. 4) showed an enlarged heart with the apex pointing toward the left, a convexity in the region of the pulmonary artery segment, and a right aortic arch. Gastrointestinal series (Fig. 5) demonstrated that the esophagus descended to the left of the midline, crossed to the right at the level of the eleventh thoracic vertebra, and entered a right-sided stomach. The pyloric antrum pointed toward the left. Barium enema (Fig. 6) revealed a right-sided sigmoid and descending colon with the transverse colon extending across the midline and returning to the right lower quadrant to join an incompletely rotated cecum.

Fig. 3.—Vectorcardiogram revealing displacement of the QRS loop superiorly, to the right, and anteriorly. The P loop is oriented anteriorly. The T loop is inscribed in a direction opposite to that of the QRS loop.

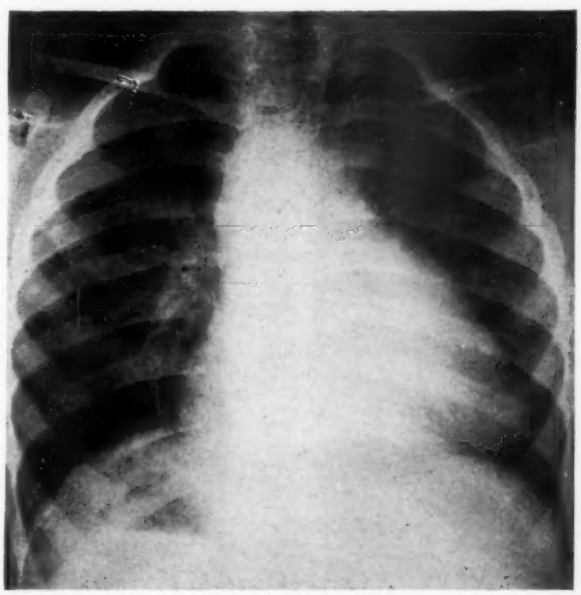

Fig. 4.—Roentgenogram of the chest showing the heart enlarged to the left, with the ventricular apex tilted upward. There is a right aortic arch.

An angiocardiogram (Fig. 7) was performed and interpreted by Drs. Marcy L. Sussman and Sigmund A. Brahms. Diodrast was introduced through a right antecubital vein and films were exposed in the posteroanterior projection. The dye entered the heart through a right superior vena cava and the first atrium to be filled extended to the left of the midline. Diodrast refluxed into the hepatic veins and the inferior vena cava, each of which entered this same left-sided atrium as a separate trunk. In the next film the contrast substance had opacified the opposite atrium,

having passed through an interatrial septal defect, and dye had entered a large ventricle. The aorta was now visualized arching toward the right and descending to the right of the midline. The main pulmonary artery was not clearly visualized, but small right and left branches were recognizable.

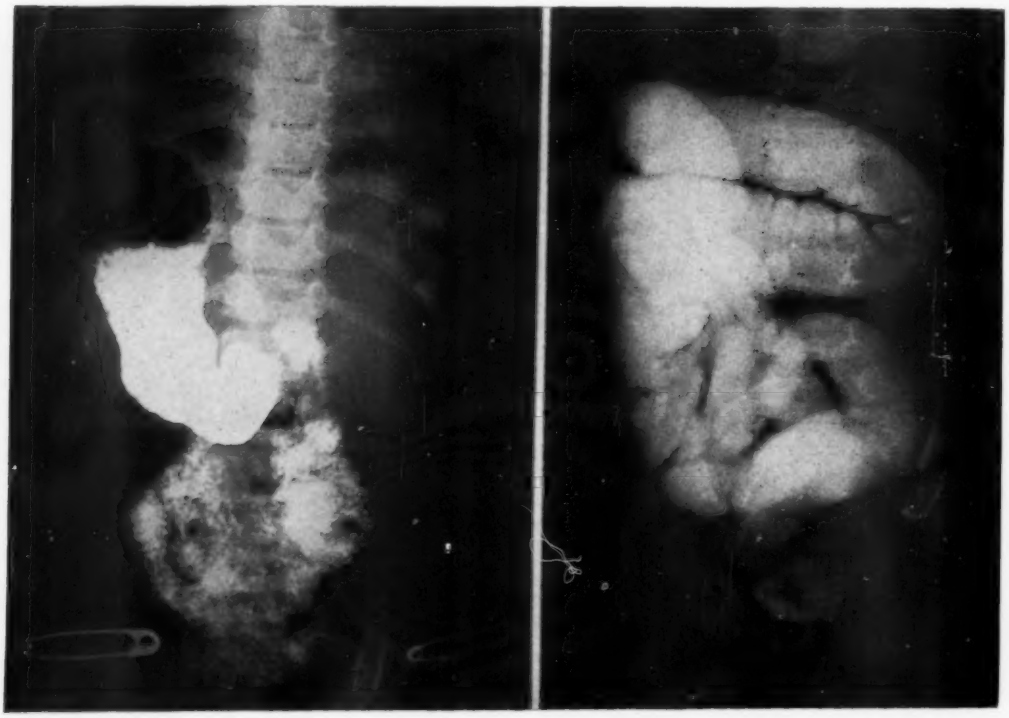

Fig. 5. Fig. 6.

Fig. 5.—Gastrointestinal series demonstrating situs inversus of the stomach and small intestine.
Fig. 6.—Barium enema showing the right-sided descending colon and the incomplete rotation of the cecum.

Cardiac catheterization was performed through the right saphenous vein. Both atria, a left superior vena cava and a right pulmonary vein were entered, (Fig. 8), but the catheter could not be manipulated into the ventricles. The spot film taken with the catheter in both a left-sided superior vena cava and a left inferior vena cava demonstrated that the systemic atrium was to the left of the midline. Catheterization of the pulmonic vein signified that either an interatrial septal defect was present, or that a pulmonic vein was inserted aberrantly into the systemic auricle. The results that were obtained from the catheterization are shown in Table I.

TABLE I.

SITE	O_2 CONTENT (VOL. %)	O_2 SATURATION (%)	PRESSURE (mm. Hg)
Superior vena cava	12.1	56.6	0
Inferior vena cava	14.2	66.4	0
Left atrium	13.2	61.6	−2
Right atrium	12.5	58.4	−2 to +2
Right pulmonic vein	19.5	91.0	4
Femoral artery	12.0	56.0	
Oxygen capacity	21.4		

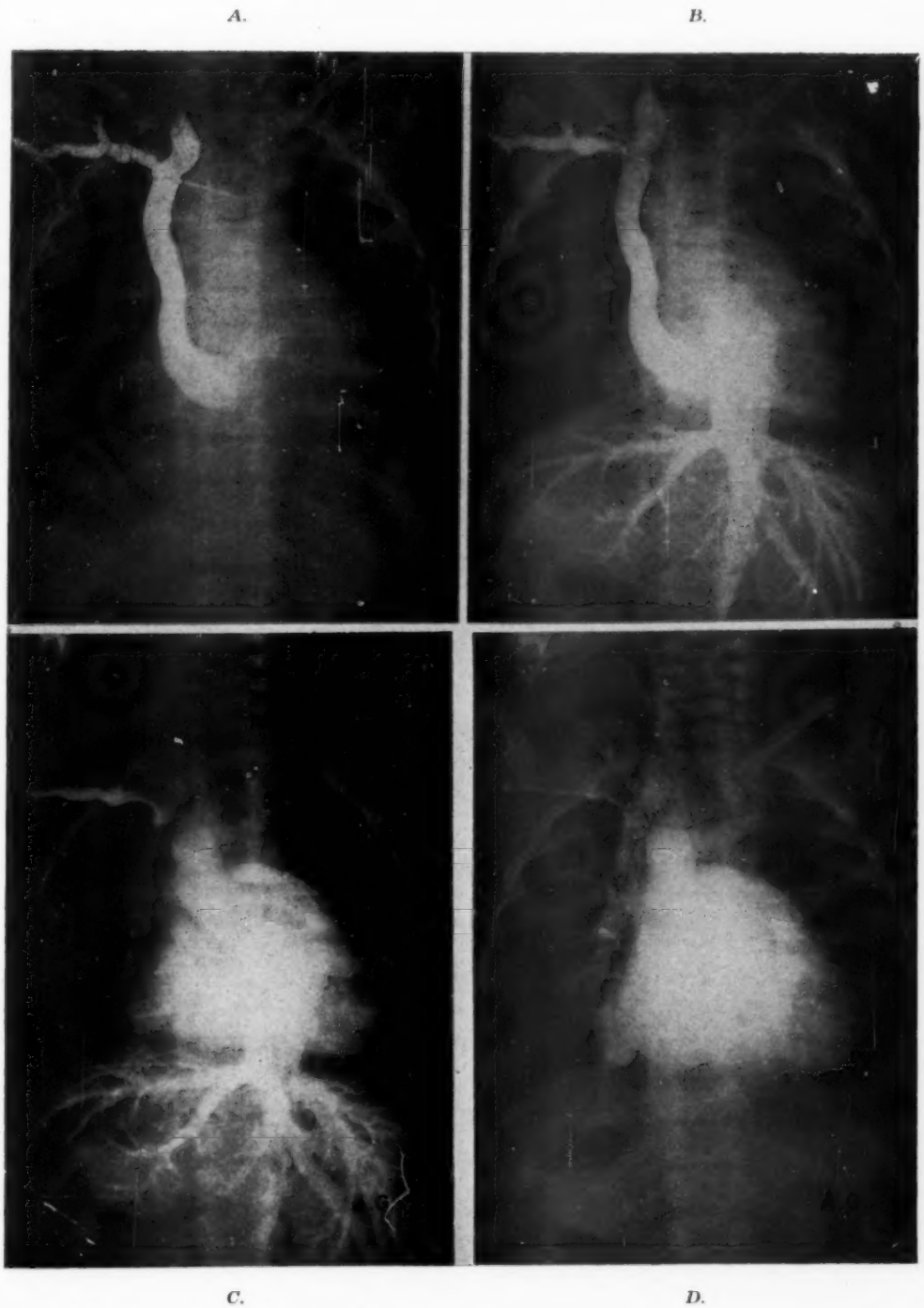

Fig. 7.—Angiocardiogram.

A, Opacification of the right-sided superior vena cava which crosses the midline to enter the left atrium.

B, The reflux of dye into the hepatic veins and inferior vena cava which enter the left atrium as separate trunks.

C, The right atrium has filled through an interatrial defect and the ventricle is visualized.

D, The right aortic arch and descending aorta and pulmonary artery branches are opacified.

The child was discharged from the hospital with the tentative diagnosis of pulmonic stenosis with a huge interatrial septal defect. It was not clear, at that time, whether or not the aorta overrode the septum. At this time, this case was included in a report on a group of cases with pulmonic stenosis with reversed interatrial shunt by Sussman and associates.[6]

The child did not improve during the subsequent one and one-half years, growing only slowly, and showing the same tendency to marked fatigue on the slightest exertion. The cyanosis remained severe. In January, 1951, at the age of 4 years, she was readmitted to the hospital for further study. Her physical condition was little changed except that the polycythemia was even more marked than on the previous admission. The hematocrit was 75 per cent, the hemoglobin level was 22 grams per cent, and the red cell count was 10.8 million per c.mm.

Cardiac catheterization was repeated. The catheter now entered both atria, a ventricle, and the pulmonary artery (Fig. 8). The results obtained are shown in Table II.

TABLE II.

SITE	O_2 CONTENT (VOL. %)	O_2 SATURATION (%)	PRESSURE (mm.Hg)
Superior vena cava	14.05	53.7	5/3
Left atrium	15.61	59.7	5/2
Right atrium	23.07	88.0	10/4
? Right ventricle	18.37	70.0	85/0
Right pulmonary artery	16.35	62.5	5/2
Oxygen capacity	26.00	———	———

A second angiocardiogram was performed and on this occasion the left anterior oblique position was used. An interatrial septal defect was again demonstrated. The aorta was prematurely visualized.

Since the second cardiac catheterization had established the presence of pulmonic stenosis, and since it seemed probable that the aorta overrode the ventricular septum, it was thought that a subclavian-pulmonary artery anastomosis would be beneficial. As a prelude to operation, several small phlebotomies were performed, in an attempt to reduce the severe polycythemia. On the day of operation a vein in the leg was being exposed. During this procedure the child had a generalized convulsion and developed a right hemiplegia and became comatose. She never regained consciousness and died several days later.

Post-morten examination was performed by Drs. Gabriel Godman and Joan Eliasoph. Upon opening the abdominal and thoracic cavities, a virtually complete situs inversus, excluding the heart, was found. The left lung consisted of three lobes while the right had two. The heart was to a large extent in the left chest, the ventricular apex pointing to the left. The great vessels at the base of the heart were transposed, with the aorta arising anterior to and slightly to the right of the pulmonary artery. The aorta arched to the right and posteriorly, giving rise, in order, to a left innominate artery, a right common carotid artery, and a right subclavian artery. The aorta descended on the right side of the vertebral column. Two superior venae cavae were present; both entered the left atrium. The inferior vena cava entered the left atrium to the left of the vertebral column. Two large defects were found in the interatrial septum. The superior defect was a large patent foramen ovale, measuring 1.5 cm. in diameter. The inferior portion of the septum was incomplete, its lower border being represented by a sharp crescentic line, 1.5 cm. superior so the atrioventricular orifice. This was thought to be a persistent ostium primum. The coronary sinus could be probed through its opening in the left atrium. Four pulmonary veins entered the right atrium. The anatomic findings were typical of transposition of the atria.

The two atria entered a common ventricular chamber that was guarded by a single, three-cusped valve. The ventricular wall was of uniform thickness and measured 1.0 cm. in width. There was no recognizable interventricular septum. However, a thick 2 cm.-wide muscular ridge extended from the anterior, inferior wall of the common ventricle and ran along the posterior wall to terminate in a fibromuscular attachment to the left wall of the ventricle. A probe could be

passed beneath this muscular column, permitting free communication of the ventricular cavity behind this ridge. The muscular ridge, in all probability, represented a rudimentary interventricular septum. No blind chamber could be found. The aortic valve was located directly to the right of the origin of the pulmonary artery (Fig. 9). Its circumference was not enlarged and there were three normally formed aortic cusps. There was no left coronary ostium. The right coronary ostium was normally located, giving rise to a common coronary artery, which bifurcated immediately beyond its origin into a right and left coronary artery. The left branch traveled in a sulcus behind both the aorta and pulmonary artery to supply the left border of the heart.

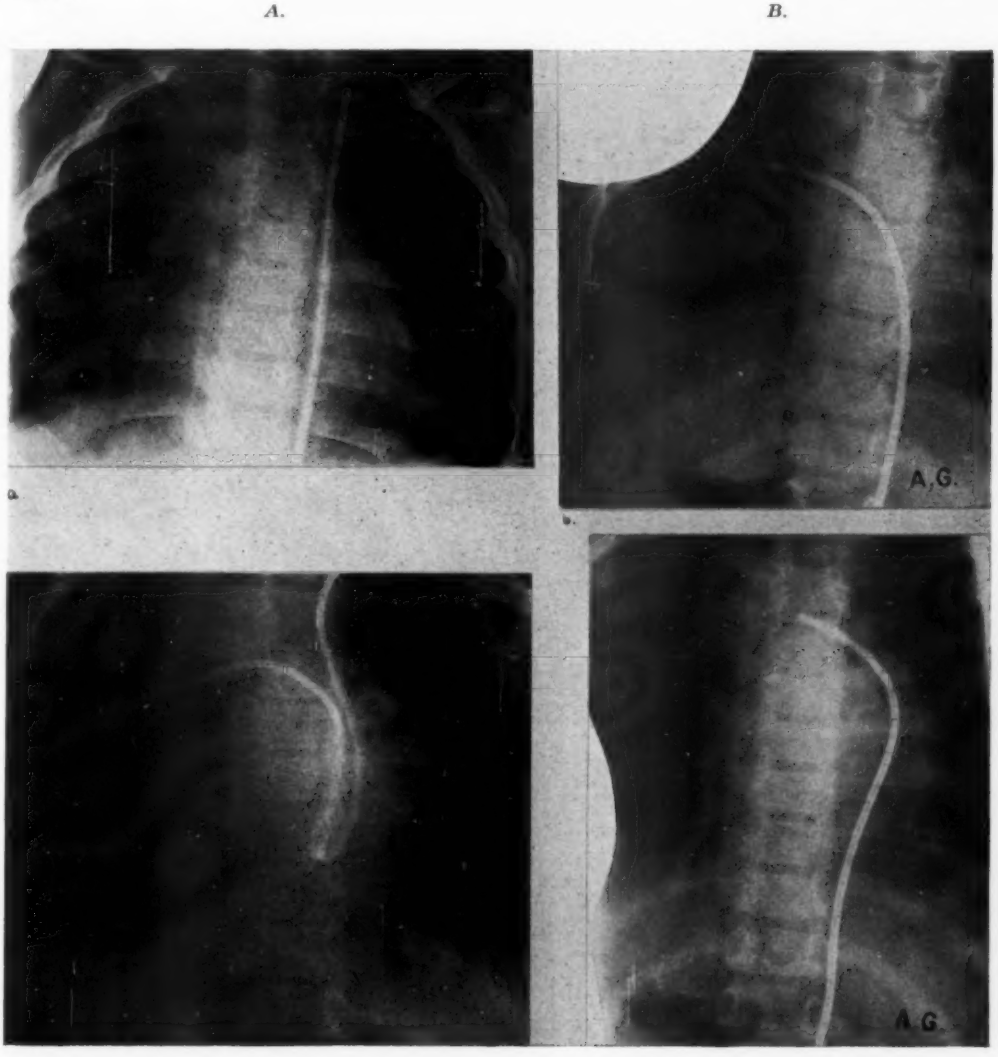

Fig. 8. Summary of the spot films taken during both cardiac catheterizations.

A, The catheter has entered the left atrium through the inferior vena cava and extends into the superior vena cava.

B, The catheter tip has entered a right pulmonic vein, having crossed into the right atrium through an interatrial septal defect.

C, and *D*, Catheter in the right pulmonary artery. These films demonstrated the left-sided position of the pulmonary artery orifice, suggesting transposition of the great vessels.

The orifice of the pulmonary artery was found above a narrow muscular recess, 1 cm. posterior to and to the left of the aortic valve. The pulmonary artery orifice was markedly stenotic, measuring 5 to 6 mm. in diameter. Two thick, fleshy excrescences represented rudimentary pulmonic cusps. Above the valve area, the pulmonary artery widened to measure 2.5 cm. in circumference, and branched into a right and left pulmonary artery. The ductus arteriosus was not patent. The flow of blood is depicted diagrammatically in Fig. 10.

The abdominal viscera were disposed in mirror-image relationship to the normal, the liver being on the left, and the spleen on the right. The mesentery of the small intestine originated to the right of the midline at the level of the second lumbar vertebra and ran diagonally to the left. The esophagus entered a right-sided stomach and the pyloric antrum pointed toward the left. The descending colon was on the right but the cecum was incompletely rotated, occupying a midline position.

Summary of autopsy findings.—Situs inversus with levocardia; transposition of the atria; common ventricle with rudimentary septum; transposition of the great vessels with pulmonic stenosis; anomalous distribution of the coronary arteries; patent foramen ovale, and persistent ostium primum.

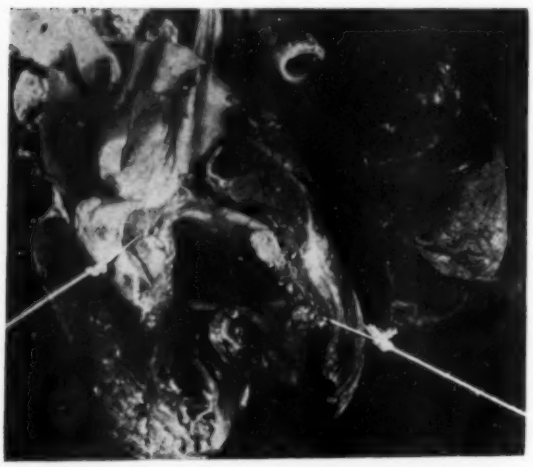

Fig. 9.

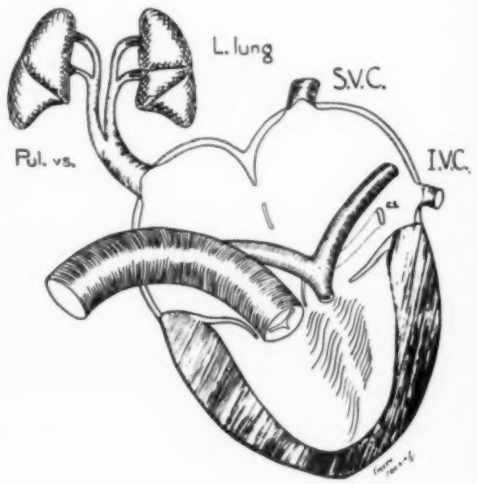

Fig. 10.

Fig. 9.—Post-mortem specimen of opened heart, in the position in which it lay when the chest was opened. The common ventricle can be seen communicating with the transposed aorta on the right and the stenosed pulmonary artery on the left.

Fig. 10.—Diagram of blood flow demonstrating the common ventricle and corrected transposition of the great vessels.

I.V.C., Inferior vena cava. *S.V.C.*, Superior vena cava. *C.S.*, Coronary sinus. *Pul. vs.*, Pulmonic veins.

COMMENT

Since levocardia is to the patient with total situs inversus what isolated dextrocardia is to the normal person, an understanding of the embryology and the various types of dextrocardia is essential to the study of a case of levocardia. The dextrocardia of total situs inversus occurs very early in embryonic development, not later than the tenth to fifteenth day, when the S-shaped curve of the primary embryonal heart tube takes place. If a contrasigmoid rotation of the cardiac tube occurs instead of the usual sigmoid twist, mirror-image dextrocardia

results. Spemann and Falkenberg[7] experimentally produced, by mechanical means, such a contrasigmoid rotation in embryos at this stage. This type of dextrocardia is characterized by inversion of the cardiac chambers, inversion of Lead I of the electrocardiogram, and has been termed Type I by Steinberg, Grishman, and Sussman,[8] who modified the original classification of Mandelstamm and Reinberg.[9] It is conceivable that some of the cases regarded as examples of levocardia follow such an embryonic development until somewhat later the heart alone rotates back to the left.

If only the heart is involved in this abnormal embryologic pattern, and there is no transposition of the viscera, "isolated dextrocardia" results. This is the mirror image of a true levocardia, and has been termed Type II by the above-mentioned authors. Isolated dextrocardia is an extremely rare condition and a true levocardia is even more uncommon. The case reported here is not one of true levocardia for several reasons: (1) there is a right-sided aortic arch; (2) there is inversion of the atria, and (3) there is transposition of the great vessels. Whether or not the ventricles were inverted could not be ascertained because of the absence of the interventricular septum and the presence of a single atrioventricular valve.

In the other two types of dextrocardia, III and IV, there is no mirror image of the cardiac chambers and no inversion of the leads of the electrocardiogram. The heart occupies a position to the right of the midline due to developmental or acquired intrathoracic abnormalities which tend to displace the heart. Occasionally the normal fetal midline position of the heart can be confused with dextrocardia.

In reviewing the collected cases of levocardia in which there has been postmortem study, Forgacs[2] was impressed by the relatively high frequency of transposition of the atria. He felt that this might be the key to the embryogenesis of levocardia. This hypothesis, modified after that of Lochte,[10] states that if the left horn of the sinus venosus, rather than the right horn, as in the normal embryo, receives the blood from the abdominal viscera, it will become incorporated into the left atrium, and a left-sided inferior vena cava will persist. Transposition of the atria will then be a necessary sequel to these events, with the left atrium receiving the systemic venous return and the pulmonic veins draining into the right atrium. A left-sided heart will then develop in the presence of situs inversus of the abdominal viscera. Thomson[4] has criticized both the theory and Forgacs' interpretation of some of the autopsy material, and feels that, although atrial transposition may be etiologically related to some of the cases of levocardia, its general application is not acceptable. The case reported here is an excellent example of atrial transposition with the left atrium receiving both the caval and coronary sinus blood while the pulmonic veins drain into the right atrium.

Our knowledge of the embryologic development of transposition of the great arterial trunks is to a large extent due to the original work of von Rokitansky,[11] Lochte,[12] and Spitzer,[13] more recently modified by Lev and Saphir,[14] and Harris and Farber.[15] The septum formation of the primitive heart tube in the mammalian heart must not only separate the pulmonary and systemic circuits but also cross these circuits so that the systemic venous return will enter the pulmonary artery and the oxygenated blood will pass out the aorta. A straight septum could only cause the circuits to exist side by side, as in the case of complete transposition.

There are two basic forms of transposition. In situs solitus (left-sided heart), the spiraling of the pulmonary artery about the aorta in a clockwise direction is deficient, and results in a right anterior position of the origin of the aorta. This was the position of the aorta with respect to the pulmonary artery in this case. In situs inversus (dextrocardia Types I and II) the spiraling is in a counterclockwise direction and insufficient torsion leaves the origin of the aorta in a left anterior position. Since this was not the situation of the great vessels in the case reported here, it cannot be regarded simply as a case of total situs inversus, in which the heart rotated back to a left-sided position at some later date.

Corrected transposition is the situation in which the transposed pulmonary artery arises from the ventricle receiving the systemic venous blood, and the transposed aorta originates from the ventricle receiving the pulmonary blood. This case demonstrates an example of corrected transposition, since the pulmonic veins drained into the auricle and ventricle leading to the transposed aorta, and the venae cavae and coronary sinus led to that side of the heart giving rise to the transposed pulmonary artery. The absence of an interventricular septum and the presence of only a single atrioventricular valve makes it difficult to determine if the ventricles were also transposed. However, the left-sided coronary sinus indicates atrial transposition. Lochte[12] in 1894 pointed out that the position of the great vessels in corrected transposition in situs solitus is identical with that in ordinary transposition in situs inversus. He believed that the inversion of the bulboventricular loop coupled with the usual type of transposition was the cause of corrected transposition.

Spitzer[13] has studied the arrangement of the coronary arteries in transposition of the great vessels. His theory explains clearly the anomalous coronary artery distribution, as was found in this case. As detorsion takes place and the aorta winds about the pulmonary artery in a counterclockwise direction, the right coronary stem will successively cross branches of the left. As it does, these branches may acquire secondary union with the right coronary artery, which originates from the right coronary cusp of the aorta and then bifurcates to supply both aspects of the heart. The coronary artery distribution of the heart described in this case follows exactly this course. A review of the reported cases of single coronary artery has been written by Smith.[16]

Young and Griswold[5] in reporting eight cases of levocardia (two of which have autopsy reports), treated by the Blalock-Taussig operation, emphasize the frequency of occurrence of both transposition of the atria and of the great vessels, leading to a corrected transposition. It is conceivable that longevity could be far greater and cyanosis milder if the septa were anything but rudimentary in such cases. Complicated additional congenital cardiac anomalies are the rule rather than the exception when levocardia is present, and the ante-mortem diagnosis may be exceedingly difficult.

Vectorcardiographic studies added considerable interest to the clinicopathologic interpretation of this case. Despite the absence of an anatomic separation of the ventricular chambers, the uniform hypertrophy of the wall of this univentricular heart had shifted the cardiac spatial vector far into the right anterior and superior position which we have come to recognize as that of right ventricular

hypertrophy.[17,18] The markedly anterior orientation of the P loop emphasized the fact that slight shifts in the position of this loop, to the left or to the right, cou'd produce an inverted or an upright P wave in Lead I. Inversion of the P wave in Lead I which was found in some of the records should not be regarded as an indication that the spread of the excitation wave over the atria in this case was similar to that encountered in cases of dextrocardia.

SUMMARY

1. A case of levocardia, or left-sided heart in the presence of situs inversus of the viscera, is presented.

2. Repeated cardiac catheterization and angiocardiograms failed to reveal all the anomalies.

3. An electrocardiographic and vectorcardiographic analysis of the case is given. The embryology of the various anomalies is considered.

4. Post-mortem findings were: levocardia with situs inversus, corrected transposition of the great vessels, single ventricle, interatrial septal defects, pulmonic stenosis, and anomalous distribution of coronary arteries.

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UNCOMPLICATED ISOLATED DEXTROCARDIA ("DEXTROVERSIO CORDIS" TYPE)

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THE VARIOUS types of isolated dextrocardia were described clearly and with diagrams by Paltauf[1] in 1901. During the first two decades of this century the German literature abounded with reports of cases of this anomaly. Mandelstamm and Reinberg[2] presented a classification of dextrocardia that is often used, although the classification that was given by Lichtmann[3] properly emphasizes the existence of various subcategories of dextrocardia that are determined by the arrangement of the great vessels.

Our report presents the results of a study of cases of right-sided hearts in which there was no inversion of the cardiac chambers and in which the heart was normal functionally. This paper emphasizes the variations in the electrocardiographic picture that may be encountered in this cardiac anomaly, particularly those variations seen in tracings obtained by use of precordial leads. In addition, we hope to focus further attention on this cardiac anomaly and to emphasize that the diagnosis of dextrocardia does not necessarily imply a functionally abnormal heart.

The hearts which we studied would belong in the group designated originally by Paltauf as "dextroversio cordis." Paltauf would not have classified these hearts as dextrocardia because this term was limited to describe hearts in which inversion of the cardiac chambers was present. He reserved the term "dextroversio cordis" for right-sided hearts in which the chambers were normally arranged. Perusal of Taussig's[4] text leads us to conclude that she would, in general, concur in this differentiation and would prefer the designation of incomplete rotation of the heart in these cases without including them in the group of true dextrocardia.

During the past fifteen years at the Mayo Clinic, twelve instances of isolated dextrocardia occurring in patients more than 10 years of age have been noted. These are contained in a total of approximately 100 cases of dextrocardia. Of the patients with isolated dextrocardia, five were cyanotic, three of them severely so; the aortas of these three were clearly on the right, producing a mirror-image heterotopia. Two patients with isolated dextrocardia displayed a defect, believed clinically to be an atrial septal defect, which did not produce cyanosis. The other five patients had no discernible abnormality in cardiac function and it is this latter group with whom our report is particularly concerned. These figures obviously do not indicate the incidence of various types of dextrocardia in a gen-

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eral population but reflect only the incidence of such individuals seeking medical care. The over-all occurrence of dextrocardia relative to total new adult registrants at the clinic is approximately one in 8,000.

During the period covered by our study, eighty-eight cases of complete situs inversus were encountered. In thirteen of this group the chief symptoms were related to bronchiectasis. Experience at the clinic with the relationship of situs inversus and bronchiectasis (Kartagener's syndrome) has been discussed by Olsen.[5] None of this group of persons with situs inversus happened to have a demonstrable gross cardiac defect. One patient did, however, have a Wolff-Parkinson-White syndrome; this case has been reported by Bartholomew and Burchell.[6] Two young children displaying situs inversus and severe congenital cardiac defects were encountered during this period of fifteen years. In this same period of time three cases of situs inversus viscerum were recorded and one case has been studied of isolated levocardia associated with a defect that caused severe cyanosis.

Of the five patients who had normally functioning right-sided hearts without situs inversus, the aortic arch and descending aorta were on the left side in all; it was thought probable that the pulmonary arterial bifurcation occupied its normal position to the left of the aorta. This relationship is clearly demonstrated by the angiocardiograms to be demonstrated in our first case report. Except for this first case, it cannot be said that the possibility of corrected transposition of the great vessels has been excluded. The electrocardiographic exploration was incomplete in one of our cases, that of a healthy woman 46 years of age; therefore, this case is not to be discussed further. However, the roentgenologic appearance in this case was exactly the same as that seen in Case 1.

CASE REPORTS

CASE 1.—A boy, 15 years of age, had been told a year previously, after a routine roentgenogram of the thorax, that his heart was out of place. He had always been active and free of symptoms.

General examination at the clinic disclosed no significant findings except that maximal intensity of the first heart sound was in the region of the xyphoid. No cardiac murmurs were detected. Hepatic dullness was in normal position. His height was 58 inches (147 cm.), and his weight was 97 pounds (44 kilograms). The results of routine laboratory tests on the urine and blood were within normal limits.

A roentgenogram of the thorax and electrocardiograms are shown in Fig. 1 and angiocardiograms are illustrated in Fig. 2,*A* and *B*.

CASE 2.—A nun, 45 years of age, registered at the clinic for evaluation of an asymptomatic hypertension that had been discovered twenty months previously. At 28 years of age she had experienced an illness characterized by sore throat, fever, painful joints, and an irregular, erythematous dermatitis of the legs. At this time she was told that she had dextrocardia but that there were no murmurs. She had noted occasional severe colds and her physician considered that mild bronchiectasis possibly was present; however, complete investigation of this possibility was not deemed necessary.

General examination at the clinic revealed that her height was 61 inches (155 cm.) and her weight was 121 pounds (55 kilograms). Blood pressure varied from 165 to 200 mm. Hg systolic and from 105 to 110 diastolic. A high-pitched squeaky murmur of moderate intensity was noted. This was heard with maximal intensity at the right edge of the sternum. It was considered

that this murmur was related to an acquired lesion of the aortic valve. Results of routine laboratory tests on the urine and blood were within normal limits.

A roentgenogram of the thorax and electrocardiograms are shown in Fig. 3.

CASE 3.—A physician was first seen at the clinic in 1939 at the age of 32 years for a routine physical examination. An isolated dextrocardia had been known to have been present but he never had noted disability or cardiac symptoms. The blood pressure had always been normal. He has been able to pursue an active practice and to serve in military service without difficulty.

The electrocardiograms and a roentgenogram of the thorax are shown in Fig. 4.

CASE 4.—A man, 36 years of age, registered at the clinic because of fatigability and transient episodes of faintness without loss of consciousness.

General examination at the clinic disclosed nothing abnormal. His height was 63.5 inches (162 cm.) and his weight was 165 pounds (75 kilograms). Blood pressure was 120 mm. Hg systolic and 90 diastolic. His symptoms were considered to be nonorganic in origin. Results of routine laboratory tests on the blood and urine were within normal limits.

The electrocardiograms and a roentgenogram of the thorax are shown in Fig. 5.

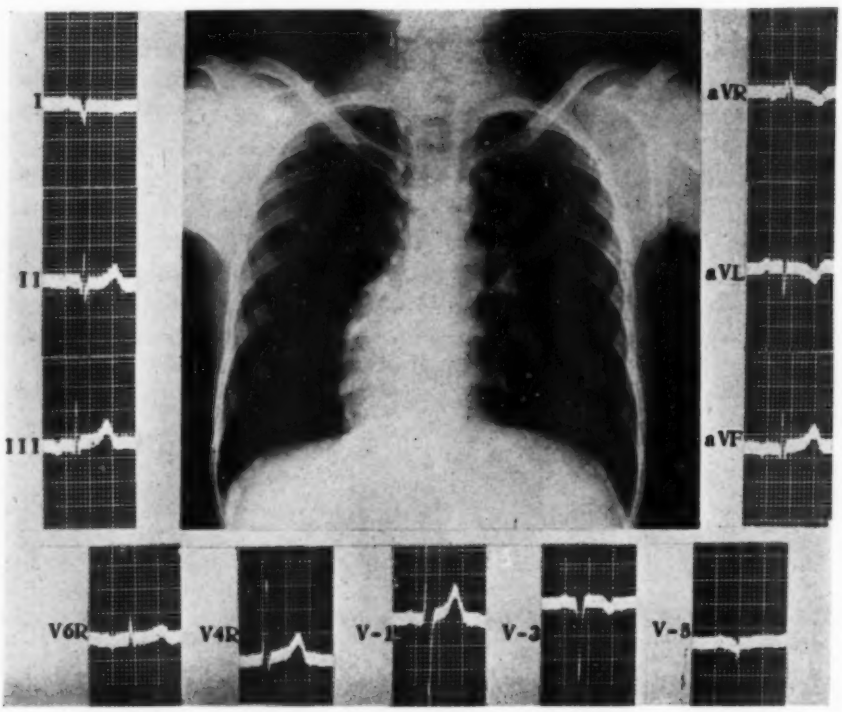


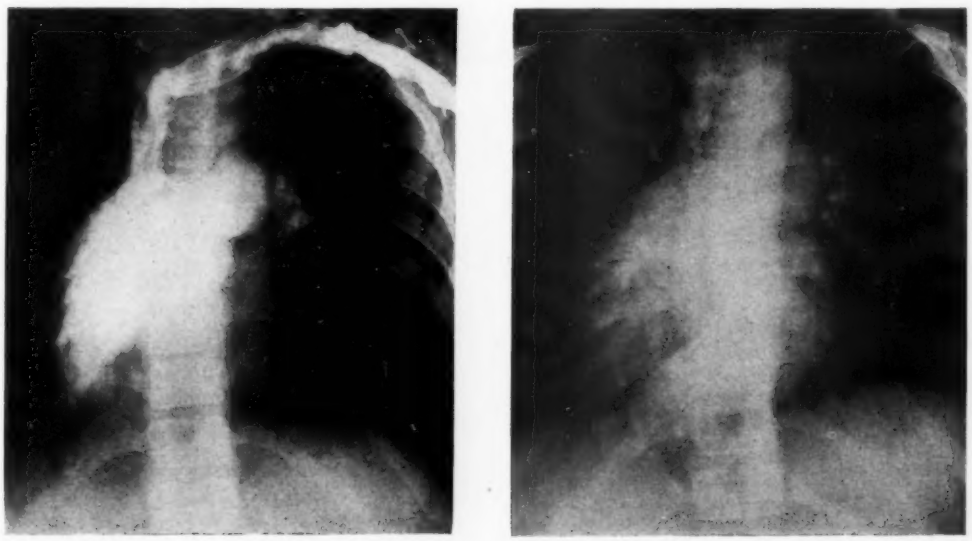
Fig. 1 (Case 1).—Electrocardiograms and thoracic roentgenogram. Note form of QRS complex in the precordial leads, in which leads from the left side of the precordium are of the QS type. Reference to the angiocardiograms in Fig. 2 will reveal the extreme dextroversion of the heart with the apex of the left ventricle lying well toward the right.

COMMENT

Study of these cases further emphasizes the fact that dextrocardia without inversion of the chambers may be associated with a functionally normal heart. Perhaps the two most carefully documented anatomic studies that have been reported on hearts without inversion of the cavities are those by Per Arén[7] and Hellmer.[8] These two reports deal with cases that are similar considering relation-

ship of the cavities of the heart but that are different considering relationship of the great vessels at the base of the heart.

The anatomic appearance of the heart of a person 57 years of age, who died from an unrelated disease, was clearly illustrated by Per Arén. The right ventricle of this heart occupied the right side of the frontal projection and the great vessels were normally interrelated. Hellmer's case is a particularly important one because death of the patient occurred at 45 years of age from heart failure. The condition in his case is called "primary dextroversion with corrected transposition," and it is well illustrated from the point of view of both the reversed positions of the aorta and pulmonary trunk and the anomalous atrioventricular valves. It would appear that the valvular derangement might possibly have played a role in the cardiac failure. The case briefly reported by Colvin[9] might be similar to this latter case because of the cardiac enlargement that he described.



A. *B.*

Fig. 2 (Case 1).—Angiocardiograms at intervals of two and six and one-half seconds after injection of iodopyracet (Diodrast) into the left arm. The former (*A*) shows filling of the superior vena cava, right atrium and ventricle, and the pulmonary artery. The latter (*B*) shows contrast medium remaining in the pulmonary arteries and outlining the left ventricle and aorta. Note that the apex of the left ventricle seems pointed to the right. The shadows of the aorta and the pulmonary arteries present a normal relationship to one another.

Cases 5 and 6 of the series reported by Mandelstamm and Reinberg[2] are similar to the type recorded in this paper. Their two cases were those of adults with normal-sized hearts and no murmurs. Meyer's[10] case was that of an active man, 60 years of age, with severe hypertension. The electrocardiogram showed evidence of left ventricular hypertrophy, and it is similar to that illustrated in Case 2 of our report with respect to the standard electrocardiographic leads. Etchegaray and del Zar[11] performed angiocardiographic and complete electrocardiographic studies, including esophageal leads, in one patient. Electrocardiograms taken with the esophageal lead at the 50 cm. level displayed a high R wave of increased duration and a negative T wave. Such electrocardiographic findings

are perhaps unexpected in view of the probable extensive anticlockwise rotation of the left ventricle. This patient appears to be the identical counterpart of the patient reported in our Case 1.

The second case in the series described by Chapman and Gibbons[12] likewise has the typical features of dextrocardia without inversion of the chambers; complete electrocardiographic studies are included in their report. The heart of their patient was normal functionally; special studies included roentgenkymograms which showed marked pulsations (systolic contractions) of the lower border of the cardiac shadow on both right and left sides. The electrocardiograms in their case resemble closely those presented in Case 2 in the present report. Cardiac catheterization was also carried out in the case reported by Chapman and Gibbons.[12] The position of the catheter was near the right border when the tip was in the right ventricle; this picture apparently resembles the roentgenogram shown in our Fig. 6.

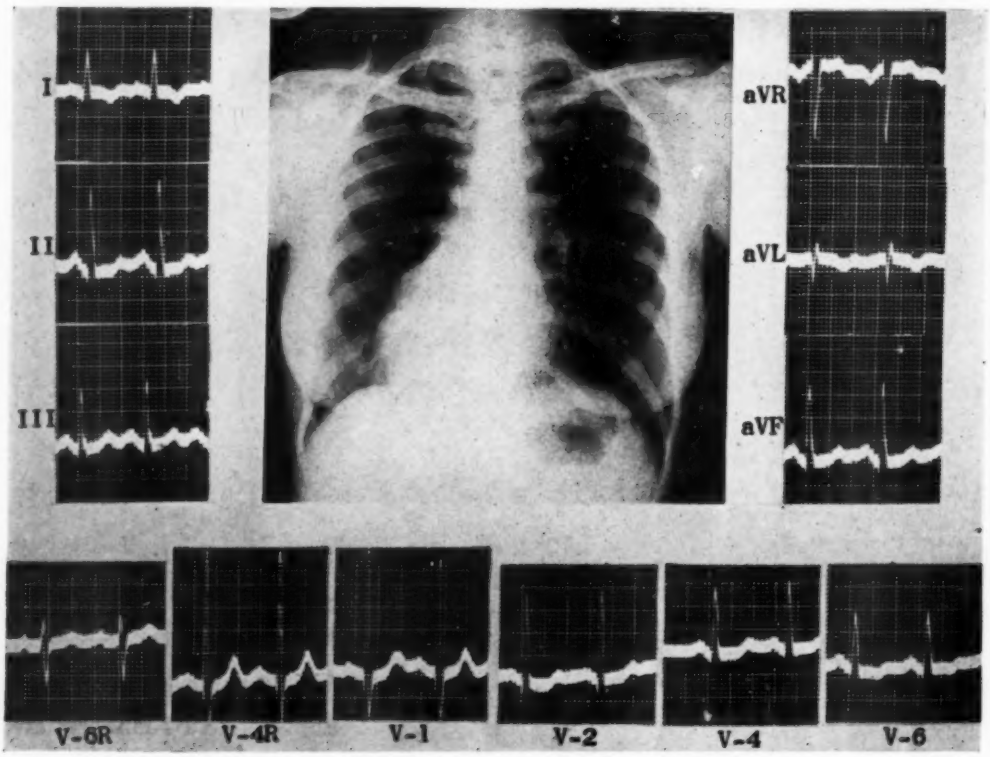


Fig. 3 (Case 2).—Electrocardiograms and thoracic roentgenogram. The patient had hypertension and probably aortic valvular disease. Electrocardiograms obtained from this patient by use of left precordial leads are similar to those obtained from patients without dextrocardia but with left ventricular hypertrophy. Note the bubble of gas in the stomach on the left.

Though the data is not convincing for all three of the cases presented by Levinsky,[13] his second case would apparently belong in the group represented by our Case 1. The third of three cases of dextrocardia reported by Jones[14] is apparently similar.

A single case of dextrocardia that had no inversion of the chambers but that probably had transposition of the vessels and an intracardiac defect has been reported by Ruskin and associates.[15] It is of particular interest because of the angiocardiographic studies. The pulmonary trunk (conus) was demonstrated on the right and the great vessels probably were transposed. Their patient was 55 years of age and had not been cyanotic. The case presented by Molari[16] would appear to be similar to the case just mentioned as to the arrangement of the great vessels, but there was no evidence of a functional defect.

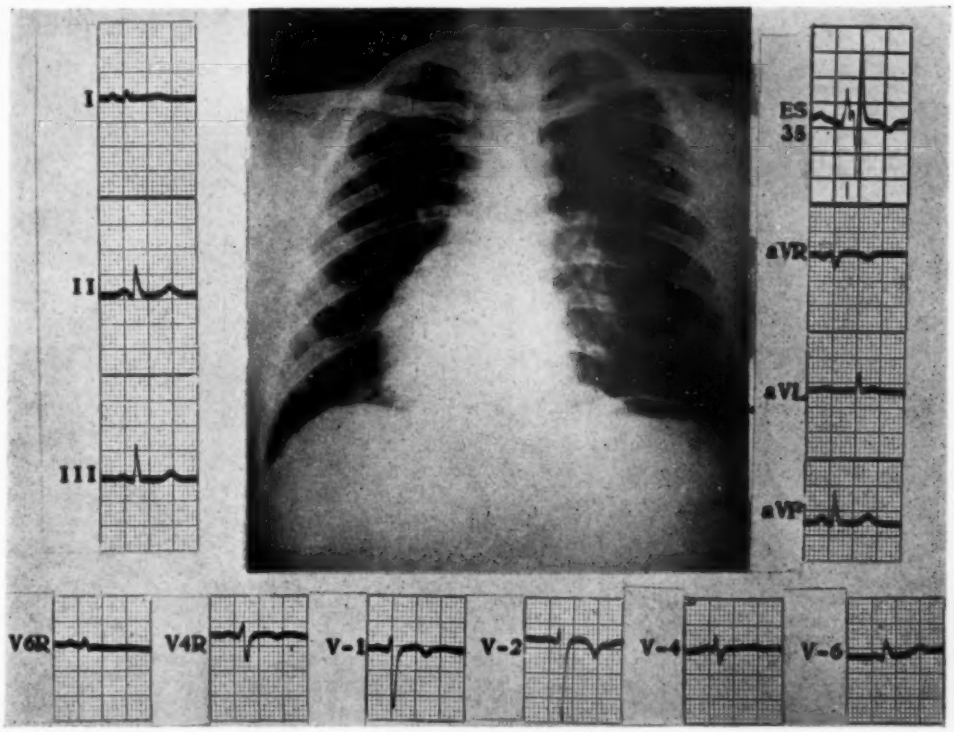


Fig. 4 (Case 3).—Electrocardiograms and thoracic roentgenogram. The approximation of the electrocardiogram to normality is to be contrasted with the striking abnormality in the roentgenogram.

The reviews on isolated congenital dextrocardia by Mandelstamm and Reinberg,[2] Rösler,[17] and Lichtmann[3] should be consulted if the subject is to be studied completely. Mandelstamm and Reinberg have presented the following classification of dextrocardia: Type I, situs inversus totalis; Type II, isolated dextrocardia with inversion of the cardiac cavities, and Type III, isolated dextrocardia with normal relationship of the chambers. Simplicity is a merit of this classification, but it is evident that variations in the arrangement of the great vessels would make mandatory some provision of subgroups in Types II and III. Such subcategories are provided in the classification arranged by Lichtmann.

ELECTROCARDIOGRAPHIC ASPECTS

The electrocardiogram obtained from a patient with isolated dextrocardia may approach normal. This is particularly illustrated in our third case (Fig. 4) in which even the left precordial records are not unusual except for the moderately low voltage, which in itself is not remarkable. The tracings in Case 4 (Fig. 5), particularly the left precordial leads, are also remarkable for their normality. It is important to note the precordial tracings in Case 1 (Fig. 1), in which the QS deflections are to the left and the R deflection is to the right. The records are designated properly and, in addition, are consistent with extremity potentials, the aVR lead having an rR deflection. Without the angiocardiogram, which showed the right ventricle on the right border, study of the electrocardiogram might have been misleading relative to the orientation of the ventricular chambers.

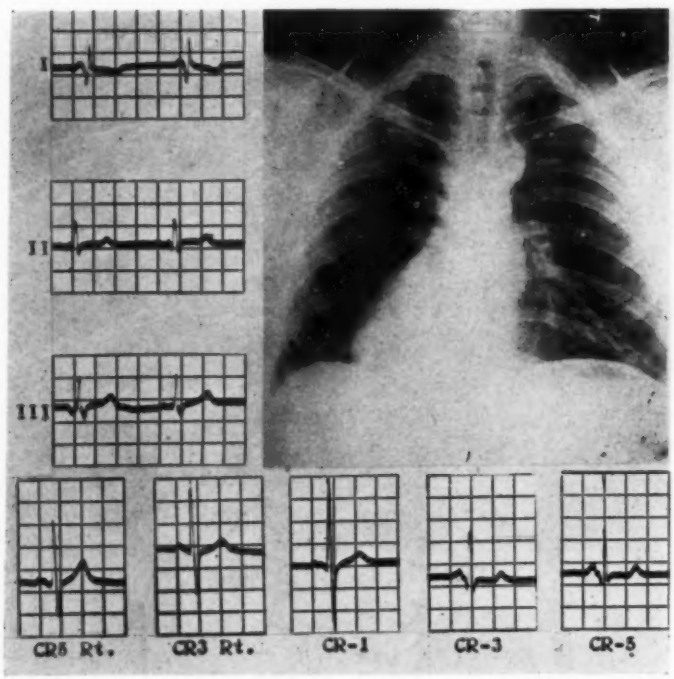
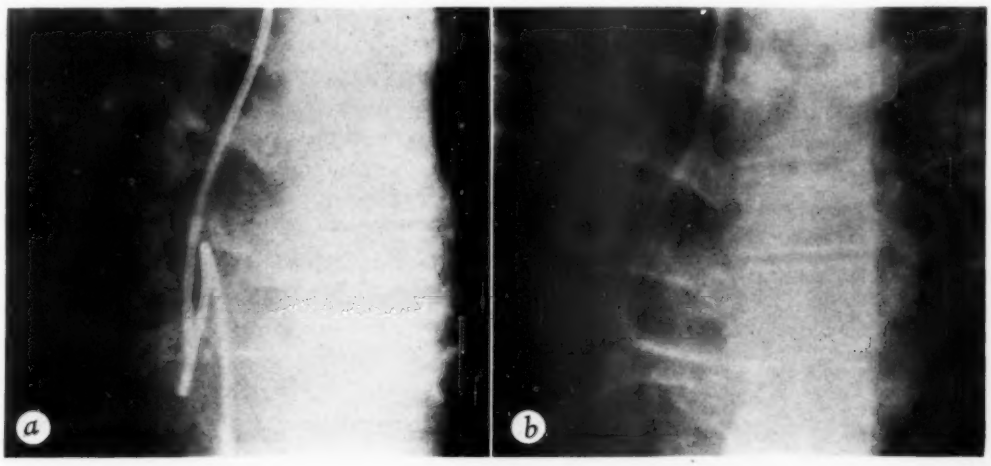


Fig. 5 (Case 4).—Electrocardiograms and thoracic roentgenogram. Tracings from the precordial leads are normal except for the high R waves produced when the electrode is on the right side of the thorax and is moved out as far as the anterior axillary line. During the inscription of impulses from the standard leads, a nodal rhythm was present. Note the small bubble of gas on the left.

The left precordial leads in Case 2 (Fig. 3) are consistent with the findings of left ventricular hypertrophy if the tracings are interpreted in the usual fashion, despite the roentgenologic demonstration of the altered position of the heart. It will be noted that this patient did have hypertension and that high R waves are present in tracings taken from the "2" position and even in those taken to the right of the sternum in the "1" position.

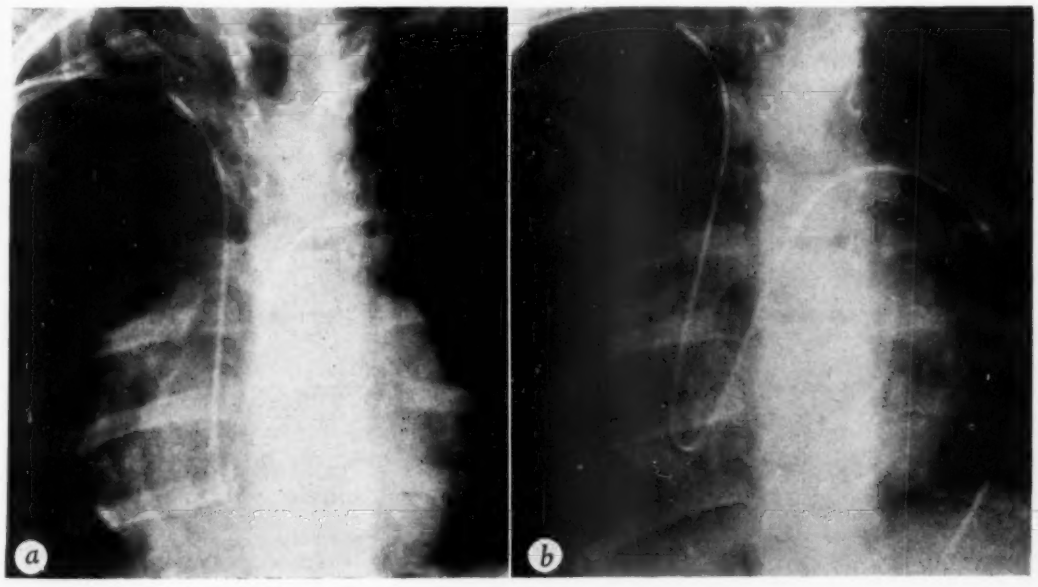
When electrocardiograms are made from patients with this type of dextrocardia, it is noted that the P wave is of normal configuration in the various leads

in the presence of sinus rhythm. This evidence indicates that the pacemaker is located in its usual position relative to the electrical activation of the atria.



A. *B.*

Fig. 6.—Roentgenograms showing a cardiac catheter coiled in the right ventricle (*A*) and in the coronary sinus (*B*). Note the normal position of the coronary sinus, with its opening to the right. This patient, 25 years of age, had dextrocardia but did not have inversion of the chambers. There was 86 per cent arterial saturation of oxygen at rest. Cardiac catheterization disclosed a right ventricular hypertension, measured as 120 mm. Hg systolic and 6 diastolic; the pulmonary artery was not entered. (Courtesy Dr. Earl H. Wood, Section of Physiology, Mayo Clinic.)



A. *B.*

Fig. 7.—Roentgenograms showing a cardiac catheter in the pulmonary artery (*A*) and in a terminal radicle of the pulmonary artery (*B*). This illustrates marked dextroposition of the pulmonary artery. The patient, 7 years of age, gave evidence of an atrial septal defect as the only functional aberration. (Courtesy Dr. Earl H. Wood, Section of Physiology, Mayo Clinic.)

SPECIAL METHODS OF STUDY

It is apparent that, if cardiac catheterization were done for patients such as those herein described, the positions of the catheter might be helpful diagnostically. None of these five patients were catheterized. However, for purposes of demonstration, roentgenograms are shown which illustrate certain positions of the catheter noted in two other patients, each of whom had isolated dextrocardia and an intracardiac defect. Fig. 6,*A* shows the catheter coiled in a right-sided right ventricle; Fig. 6,*B* shows the catheter in the coronary sinus. In the latter illustration it is apparent that the coronary sinus is in its normal position. Fig. 7,*A* and *B* shows the position of the catheter to be in the right ventricle and pulmonary artery of a patient who had partial dextroversion. Cardiac catheterization performed on this patient gave evidence of an atrial septal defect. Roentgenographically and roentgenoscopically the heart lay mainly in the right side of the thorax. The course of the right ventricular outflow and pulmonary artery, as it is outlined by the catheter, is well to the right of its normal position.

A case of apparently similar incomplete dextroversion of the heart has been reported by De Groot.[18] The main features of his report concerned the presence of bilateral superior venae cavae and a patent ductus arteriosus. His patient was an infant on whom both cardiac catheterization and angiocardiographic study were done. The latter showed the shadow of the right ventricle and pulmonary artery to be disposed in a fashion similar to that noted in angiocardiographic studies in our Case 1.

There is still lack of uniformity in reports and textbook discussions concerning these cases in which the heart is in the right side of the thoracic cavity, yet in which the chambers of the heart are not reversed. Because these cases do present themselves roentgenologically as right-sided hearts, it seems proper that they be classified as dextrocardia, but they should be placed in a special category. The classification of Lichtmann is particularly meritorious for this purpose because it places emphasis on the importance of a study of the arrangement of the great vessels at the base of the heart. In a study of these cases if often may seem justifiable to perform angiocardiographic studies or cardiac catheterization.

OTHER TYPES OF DEXTROCARDIA

Taussig[4] has emphasized the difficulty of the diagnostic problem presented by a patient with functionally complicated isolated dextrocardia. Difficulty of interpretation of the electrocardiograms obtained from these patients has been emphasized by one of us (Burchell[19]). This entity will not be considered in this presentation.

Dextrocardia with inversion of the chambers and right-sided aortic arch (situs inversus thoracis) must be mentioned as it may occasionally exist without functional abnormality. The case described by Stevenson,[20] which included post-mortem studies, seems to be the best example. Case 9 of Mandelstamm and Reinberg also appears to be an authentic example of situs inversus thoracis. The heart in this case was perfectly normal from the functional viewpoint. The case described by Jaubert de Beaujeau and Benmussa[21] is less well established be-

cause of the clinical evidence of aortic insufficiency. Situs inversus thoracis presents the mirror image of normal intrathoracic structures associated with normal position of the abdominal viscera. It may occur more frequently than the reported incidence might indicate, because its presence in asymptomatic persons may escape recognition.

Isolated dextrocardia with mirror-image arrangement of the cardiac cavities and great vessels is generally accompanied by an intracardiac defect, as emphasized by Rösler[17] and Lichtmann.[3] Isolated dextrocardia without inversion of chambers also may be accompanied by serious changes in the functional capacity of the heart. Cardiac dysfunction in anomalies of the latter type is perhaps more universally true when such anomalies are discovered in children, as judged by the report of Donzelot and associates.[22]

SUMMARY

Four cases of isolated dextrocardia without inversion of the cardiac chambers and without evidence of cardiac disability have been reported.

Electrocardiographic tracings obtained from patients with this malformation may deviate remarkably little from normal. Considerable variation was noted among the various cases in the precordial complexes, particularly in those obtained from leads over the left side of the thorax.

Angiocardiographic study or cardiac catheterization may be indicated in certain instances to ascertain the position and relationship of the great vessels at the base of the heart or to rule out the presence of an occult interatrial shunt from left to right.

The alternative simple term "dextrorotation of the heart" may be an applicable synonym in those cases which fulfill the following criteria: (1) the great vessels have a normal basic relationship, (2) the heart is normal functionally, and (3) inversion of the cavities is absent.

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CHRONIC CONSTRICTIVE PERICARDITIS: FURTHER CONSIDERATION OF THE PATHOLOGIC PHYSIOLOGY OF THE DISEASE

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CONSTRICTIVE pericarditis is a disorder of the heart often amenable to surgery, and its diagnosis and treatment therefore have immediate importance. Both diagnosis and treatment depend upon an understanding of the physiologic abnormalities associated with this disease. Within the limits of methods hitherto available, these abnormalities and the resulting symptoms and signs have been defined.[9,10] The advent of additional tools now opens new and more definitive avenues of study. The venous catheter makes it possible to investigate the pulmonary circulation, a region previously inaccessible. It is our purpose to set forth the results of observations made by the use of the venous catheter in six patients with constrictive pericarditis and in the light of these studies to reconsider certain earlier concepts. On the basis of these new studies the importance of constriction of *both* ventricles, particularly the left, will be emphasized.

MATERIAL

The diagnosis of constrictive pericarditis was made in six men. (This diagnosis was subsequently confirmed at operation.) Each of these patients was studied by venous catheterization.[1] In one patient observations were not made until eight years after cardiac decortication.

METHODS

Circulatory dynamics were studied at rest and during mild exercise. The day before the recorded studies the patients rehearsed the various procedures required of them: exercising on the bicycle ergometer in the laboratory and

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receiving instruction in the use of the mouthpiece for collection of expired air. On the day of study, they were fasted or else received a light breakfast. No sedative was administered. Cardiac catheterization was performed and the tip of the catheter placed so as to occlude a branch of the pulmonary artery. Pulmonary "capillary" pressure, as described by Hellems, Haynes and Dexter,[2] was recorded at rest (after five minutes or more of silence and inactivity, during which time pulse and respiration had become stable) and again during exercise (at the end of the second minute of a three-minute period of exercise as described below). Sufficient time was allowed between exercise periods to allow pulse and respiration to return to normal—usually at least ten minutes.

The catheter was then withdrawn to a point just distal to the bifurcation of the pulmonary artery. A No. 20 or 21 short-bevel needle was inserted into the brachial artery, the lumen of the needle being kept patent by a slow saline infusion. After pulse and respiration had returned to the initial resting level, resting cardiac output was measured by the direct Fick method. Expired air was collected for three minutes in a Douglas bag. Midway during the gas collection, blood samples were withdrawn simultaneously from the brachial and pulmonary arteries. Immediately thereafter, pressures in these arteries were recorded. Similar observations were then made during exercise. Pressures were taken after two minutes of exercise. Expired air was collected between two and one-half and three minutes and, during the collection of the expired air, blood samples were withdrawn. The volume of expired air was measured in a Tissot spirometer, and the concentration of oxygen was measured by a Pauling oxygen analyzer. Carbon dioxide was not determined. Correction was made for the change in nitrogen concentrations in the expired air, using an average RQ correction.[3] Blood samples were analyzed for oxygen content and capacity by the method of Van Slyke and Neill[4] and the arteriovenous oxygen difference calculated. In most of the patients, the catheter was then withdrawn to the right auricle where pressures were obtained at rest and after two minutes of exercise.

Pressures were measured with Hamilton manometers[5] or, in the latter part of the series, with electromanometers*[6] which recorded on a multi-channel, direct-writing oscillograph. The recording was calibrated with a mercury manometer after each pressure tracing. The zero point for all pressures was 10 cm. anterior to the back with the patient supine.[7] A saline manometer was used for checking mean pressures, but electromanometer readings were used for analytical purposes in all cases. Mean pressures were obtained by planimetric integration of the pressure tracings when using the Hamilton manometer and by electrical integration when using the oscillographic tracings. The mean pressure gradient between pulmonary artery and pulmonary "capillaries" (PA-PC) was obtained by subtraction.

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Pulmonary *arteriolar* resistance was calculated as follows:

$$Rp = \frac{PA_m - PC_m}{Q/t} \times 1332, \text{ expressed in dynes seconds cm.}^{-5}$$

Total systemic resistance was calculated as follows:

$$Rs = \frac{BA_m - O}{Q/t} \times 1332, \text{ expressed in dynes seconds cm.}^{-5}$$

when PA_m = mean pressure in the pulmonary artery in mm. Hg
PC_m = mean pressure in the pulmonary capillaries in mm. Hg
BA_m = mean pressure in the brachial artery in mm. Hg
Q/t = cardiac output in c.c. per second
1332 = the conversion factor from mm. Hg to dynes per cm.[3]

The duration of left ventricular diastole was calculated from brachial arterial pressure tracings as described elsewhere[8] and compared with our normal controls calculated in the same manner. In two instances, as indicated in Table I, a radial rather than brachial arterial pressure tracing was used.

Exercise was performed with the patient recumbent, and consisted of pedalling a bicycle ergometer at the rate of 56 r.p.m., timed with a metronome. The pedal resistance was varied from individual to individual and no attempt was made to express the external work performed. Because of variations in efficiency among different individuals, the oxygen consumption has been taken as an index of work performed.

It was judged unsafe to exercise patients with the tip of the catheter lying free in the right ventricle. Ventricular dynamics were, therefore, studied in the following manner. Continuous pressures were recorded as the catheter was withdrawn from the pulmonary artery to the right auricle. The pulmonary artery systolic and the right ventricular systolic pressures were identical in each case and the right auricular and the right ventricular diastolic pressures were the same. Therefore, in the tables, the *pulmonary artery systolic* pressure at rest and exercise is taken as a measure of the *right ventricular systolic* pressure and the *right auricular mean* as a measure of the *right ventricular diastolic* filling pressure. In the cases in which it was possible to measure the right ventricular end diastolic pressure, it differed by not more than 1 mm. from the auricular mean. Therefore, the use of the right auricular mean pressure as an approximation of the right ventricular diastolic filling pressure in these patients with constrictive pericarditis does not affect our interpretations.

Data obtained during different rest and exercise periods were treated (in figures and tables) as though the measurements had all been obtained simultaneously. This procedure is justified if all pressures and flows return to pre-exercise values before a new set of determinations is made. It is apparent from Table III that some values returned to resting levels two minutes following exercise and that all values were comparable to the original resting determinations five minutes after exercise. In practice, at least ten minutes elapsed after each exercise period before a new set of determinations was made. Therefore,

TABLE I. VOLUMES OF BLOOD FLOW AND VENTILATIONS, AND LEVELS OF ARTERIOLAR RESISTANCE IN PATIENTS WITH CONSTRICTIVE PERICARDITIS AT REST AND EXERCISE

NAME		WEEKS BEFORE (−) OR AFTER (+) OPERATION	BODY SURFACE AREA (Sq. M.)	OXYGEN CONSUMPTION (c.c./min./sq. M.)	OXYGEN SATURATION (%)	A-V OXYGEN DIFFERENCE (c.c./L.)	CARDIAC OUTPUT (L./min.)	CARDIAC INDEX (L./min./sq. M.)	STROKE INDEX (c.c./beat/sq. M.)	PULSE RATE	DURATION OF DIASTOLE (sec./min.)	VENTILATION (L./min.)	RESISTANCE (Dynes sec. cm^{-5})		RHYTHM
													PULMONARY ARTERIOLAR	TOTAL PERIPHERAL	
E. L.	R*	−1	1.68	100	98	35	4.8	2.9	39	74	32	5.8	50	1481	Regular
	Ex	−1	1.68	302	96	66	7.7	4.6	44	104	26	15.6	31	1090	
		Operation													
	R	+10	1.63	151	97	34	7.3	4.5	62	72	34	5.9	77	1183	Regular
	Ex	+10	1.63	330	96	69	7.8	4.8	45	106	27	14.1	82	1158	
	R	+50	1.63	130	99	33	6.4	3.9	53	74	35	7.3	25	1124	Regular
	Ex	+50	1.63	390	100	74	8.7	5.3	55	98	—	17.9	101	910	
E. P.	R	−1	1.60	168	99	46	5.8	3.6	38	96	34	8.5	69	1048	Auricular fibrillation
	Ex	−1	1.60	452	99	101	7.1	4.4	29	150	22	14.9	68	1082	
		Operation													
	R	+2	1.53	144	99	47	4.7	3.1	29	104	31†	6.5	34	1395	Auricular fibrillation
	Ex	+2	1.53	385	99	108	5.5	3.6	25	144	—	13.6	44	—	
	R	+33	1.57	196	100	49	6.3	4.0	61	66	—	15.1	—	1270	Regular
	Ex	+33	1.57	536	—	110	7.7	4.9	64	76	—	21.2	—	—	
C. R.	R	−2	1.74	135	98	55	4.3	2.5	25	100	34	9.7	—	1486	
	Ex	−2	1.74	423	95	117	6.3	3.6	29	126	—	15.4	76	1167	Regular
		Operation													
	R	+4	1.67	146	95	50	4.9	2.9	38	78	37	9.9	49	1565	
	Ex	+4	1.67	264	94	73	6.0	3.6	42	86	—	14.9	120	—	Regular
	R	+47	1.73	154	99	56	4.8	2.8	37	75	36	11.4	33	1249	Regular
	Ex	+47	1.73	396	92	102	6.7	3.9	43	90	32	15.0	60	1217	
H. C.	R	−10	1.82	100‡	93	67	2.7	1.5	18	84	—	—	326	—	Regular
		Operation													
	R	+33	1.68	113	94	46	4.1	2.4	38	64	—	6.9	—	—	Regular
	Ex	+33	1.68	333	91	90	6.2	3.7	37	100	—	17.0	—	—	
	R	+144	1.67	130	98	52	4.2	2.5	42	60	—	8.6	152	1750	Regular
	Ex	+144	1.67	409	97	101	6.8	4.1	46	90	—	19.0	129	1081	
L. S.	R	−46	1.64	152	98	65	3.8	2.3	28	82	—	8.1	130	1745	Regular
	Ex	−46	1.64	322	100	116	4.5	2.7	26	108	—	14.0	107	1440	
		Operation													
G. M.		Operation													
	R	+8 yr.	1.66	107‡	94	29	6.1	3.7	49	75	—	—	—	—	Regular

*R = rest. Ex = exercise.
†Radial arterial pressure tracing used for the calculation rather than a brachial arterial tracing.
‡Oxygen consumption determined by means of the Benedict-Roth metabolism machine.

the data obtained in this fashion in these individuals may be treated as though all values had been obtained simultaneously. (Variations observed in Table III have been taken into account in interpreting the results.)

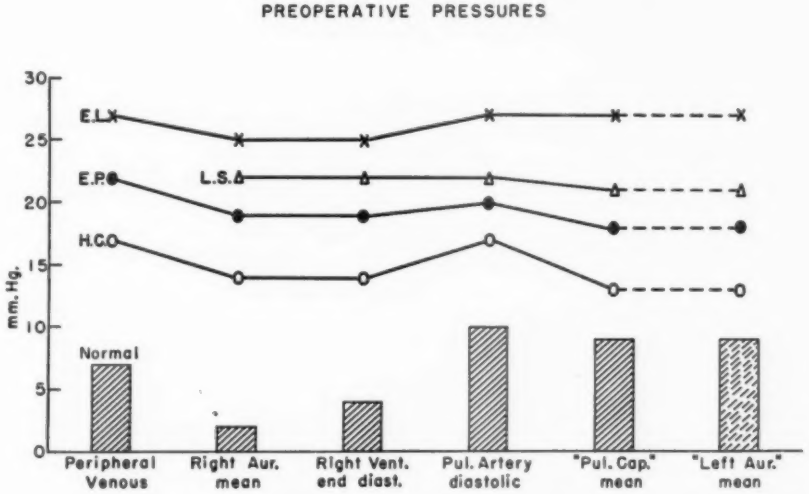

Fig. 1.—Preoperative intravascular pressure in four patients with constrictive pericarditis. The barred columns serve as an approximate standard of reference representing the average values in eight normal individuals studied in this laboratory by the same technique.[3]

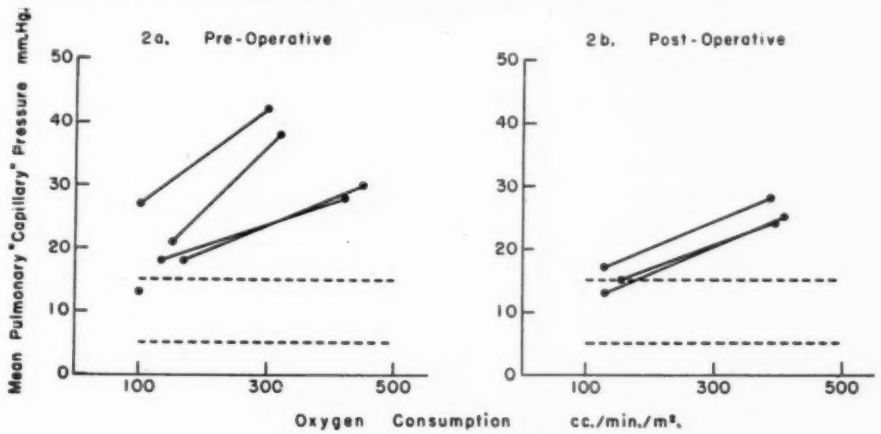

Fig. 2.—Mean pulmonary capillary pressure. In this and all subsequent figures the dotted lines serve as an approximate zone of reference representing the limits of variation seen in eight normal individuals studied in this laboratory by the same techinque.[3]

RESULTS

The data are reported in Tables I, II, and III and in Figs. 1 to 8. They deal essentially with volumes of blood flow and with the height of blood pressures in various parts of the circulatory system. Both flow and pressure were determined under conditions of rest and of exercise both before and after operation. As our normal standard, we have used the range of values observed during catheterization of normal subjects in this laboratory. When more than one study has been made after operation, the results of the latest observations are used in

*R = rest. Ex = exercise.
†Radial arterial pressure tracing used for the calculation rather than a brachial arterial tracing.
‡Oxygen consumption determined by means of the Benedict-Roth metabolism machine.

TABLE II. PRESSURES IN PATIENTS WITH CONSTRICTIVE PERICARDITIS AT REST AND EXERCISE

NAME		WEEKS BEFORE (−) OR AFTER (+) OPERATION	A-P* DIAMETER OF CHEST (Cm.)	VENOUS PRESSURES (mm. Hg)	RIGHT AURICULAR PRESSURES (MEAN mm. Hg)	RIGHT VENTRICULAR PRESSURES (mm. Hg)		PULMONARY ARTERIAL PRESSURES (mm. Hg)			PC MEAN PRESSURES (mm. Hg)	PA-PC† GRADIENT (mm. Hg)	SYSTEMIC ARTERIAL PRESSURES (mm. Hg)		
						SYSTOLIC	END DIASTOLIC	SYSTOLIC	DIASTOLIC	MEAN			SYSTOLIC	DIASTOLIC	MEAN
E. L.	R‡	−1	20	27	25	39	25	39	27	30	27	3	114	76	89
	Ex	−1	20	—	35	53	35	53	41	45	42	3	135	88	105
		Operation													
	R	+10	20	18	18	35	18	35	22	26	19	7	146	93	108
	Ex	+10	20	—	28	52	28	52	33	45	36	8	160	93	113
	R	+50	20	13	12	27	12	27	16	19	17	2	115	70	90
	Ex	+50	20	—	21	55	21	55	35	39	28§	11	149	80	99
E. P.	R	−1	18	22	19	36	19	36	20	23	18	5	112	68	76
	Ex	−1	18	—	24	—	24	—	—	36	30	6	136	88	96
		Operation													
	R	+2	18	—	14	31	14	31	17	24	22	2	110	68	82
	Ex	+2	18	—	20	—	20	—	—	35	32	3	—	—	—
	R	+33	18	13	10	29	10	29	15	20	—	—	131	80	100
	Ex	+33	18	—	13	—	13	—	—	25	—	—	—	—	—
C. R.	R	−2	19	—	19	—	19	—	—	16	—	—	108	72	80
	Ex	−2	19	—	31	—	31	—	—	34	28	6	128	72	92
		Operation													
	R	+4	19	12	10	30	10	30	20	24	21	3	128	72	96
	Ex	+4	19	—	17	43	17	43	27	32	23	9	—	—	—
	R	+47	19	12	12	27	12	27	14	17	15	2	110	62	75
	Ex	+47	19	—	23	40	23	40	22	29	24	5	146	85	102

H. C.	R	−10 Operation	18	17	14	36	14	36	17	24	13	11	80	66**	—
	R	+33	18	—	11	46	11	46	19	31	—	—	110	80**	—
	Ex	+33	18	—	17	66	17	66	27	42	—	—	—	—	—
	R	+144	18	7	6	37	6	37	14	21	13	8	134	70	92
	Ex	+144	18	—	9	61	9	61	28	36	25	11	160	70	92
L. S.	R	−46	19	—	22	33	22	33	22	27	21	6	98	68	83
	Ex	−46 Operation	19	—	27	55	27	55	40	44	38	6	115	70	81
G. M.	R	Operation +8	21	11	10	35	10	35	20	24	—	—	110	64**	—

*A-P = Anterior-posterior.

†PA = pulmonary artery. PC = pulmonary "capillary".

‡R = rest. Ex = exercise.

§Recorded value may not be true PC pressure, as oxygen saturation only 93 per cent as compared to a saturation of 100 per cent in the peripheral arterial sample.

**Peripheral arterial pressures recorded with blood pressure cuff rather than with intra-arterial needle.

TABLE III. COMPARISON OF VALUES OBSERVED AT REST AND DURING RECOVERY FROM EXERCISE

NAME	WEEKS BEFORE (−) OR AFTER (+) OPERATION	MEAN PRESSURES (mm. Hg)											
		RIGHT AURICLE			PULMONARY ARTERY			PULMONARY CAPILLARY			SYSTEMIC ARTERY		
		REST	RECOVERY		REST	RECOVERY		REST	RECOVERY		REST	RECOVERY	
			2 MIN.	5 MIN.		2 MIN.	5 MIN.		2 MIN.	5 MIN.		2 MIN.	5 MIN.
E. L.	−1 Operation	25	26	—	30	—	—	27	28	—	—	—	—
	+10	18	20	—	—	—	—	—	—	—	—	—	—
	+50	12	—	11	19	—	21	17	—	16*	90	—	90
E. P.	−1 Operation	19	17	—	23	26	—	18	18	—	76	92	—
	+2	14	13	—	24	26	—	22	23	—	—	—	—
	+33	10	—	10	20	—	16	—	—	—	—	—	—
C. R.	−2 Operation	19	19	—	16	22	—	—	—	—	80	90	—
	+4	10	12	—	24	28	—	21	16	—	96	—	—
	+47	12	—	13	17	—	21	15	—	12	75	—	77
H. C.	−10† Operation												
	+33	11	13	—	—	—	—	—	—	—	—	—	—
	+144	—	—	—	21	—	21	—	—	—	92	—	86
L. S.	−46 Operation	22	—	19	27	—	26	21	—	23	83	—	74

TABLE III. COMPARISON OF VALUES OBSERVED AT REST AND DURING RECOVERY FROM EXERCISE—CONTINUED

NAME	OXYGEN CONSUMPTION (c.c./min./sq. M.)			A-V DIFFERENCE (c.c./L.)			CARDIAC INDEX (L./min./sq. M.)			STROKE INDEX (c.c./beat/sq. M.)			PULSE (Rate/min.)			VENTILATION (L./min.)		
	REST	RECOVERY		REST	RECOVERY		REST	RECOVERY		REST	RECOVERY		REST	RECOVERY		REST	RECOVERY	
		2 MIN.	5 MIN.		2 MIN.	5 MIN.		2 MIN.	5 MIN.		2 MIN.	5 MIN.		2 MIN.	5 MIN.		2 MIN.	5 MIN.
E. L.	—	—	—	—	—	—	—	—	—	—	—	—	74	84	—	—	—	—
	—	—	—	—	—	—	—	—	—	—	—	—	72	78	—	—	—	—
	130	—	110	33	—	37	3.9	—	3.0	53	—	42	74	—	72	7.3	—	6.5
E. P.	—	—	—	—	—	—	—	—	—	—	—	—	96	104	—	—	—	—
	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	196	—	170	49	—	57	4.0	—	3.0	61	—	47	66	—	64	15.1	—	9.4
C. R.	—	—	—	—	—	—	—	—	—	—	—	—	100	87	—	—	—	—
	—	—	—	—	—	—	—	—	—	—	—	—	78	75	—	—	—	—
	154	—	169	56	—	57	2.8	—	2.9	37	—	41	75	—	72	11.4	—	10.6
H. C.																		
	113	144	—	46	51	—	2.4	2.8	—	38	33	—	64	84	—	6.9	9.0	—
	130	—	129	52	—	50	2.5	—	2.6	42	—	43	60	—	60	8.6	—	8.0
L. S.	—	—	—	—	—	—	—	—	—	—	—	—	82	—	80	—	—	—

*Recorded value may not be true PC pressure, as oxygen saturation is only 93 per cent as compared to a saturation of 100 per cent in the peripheral arterial sample.

†Not exercised when studied before operation.

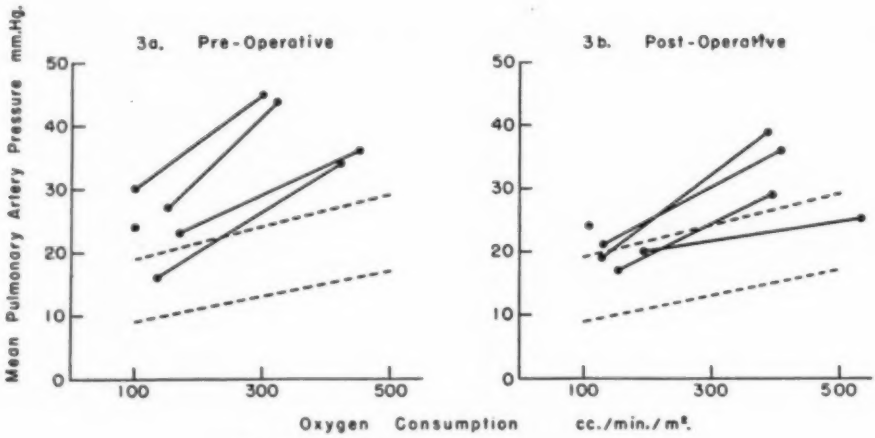

Fig. 3.—Mean pulmonary artery pressure.

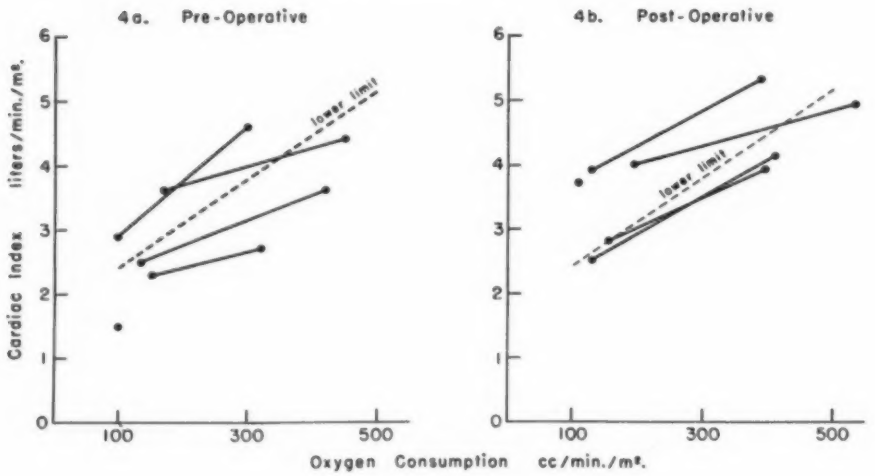

Fig. 4.—Cardiac index.

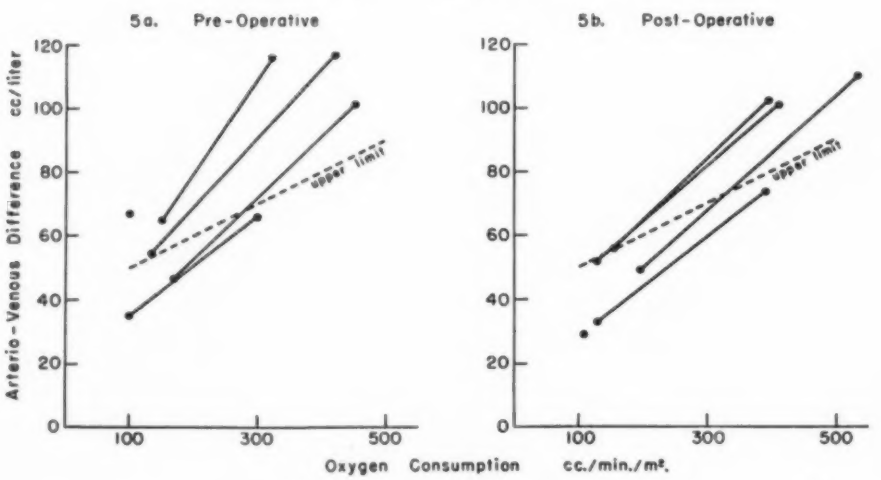

Fig. 5.—Arteriovenous difference.

the figures. For purposes of comparison the resting and exercise values in the figures are connected by straight lines. The degree of exercise is expressed as the oxygen consumption per square meter per minute.

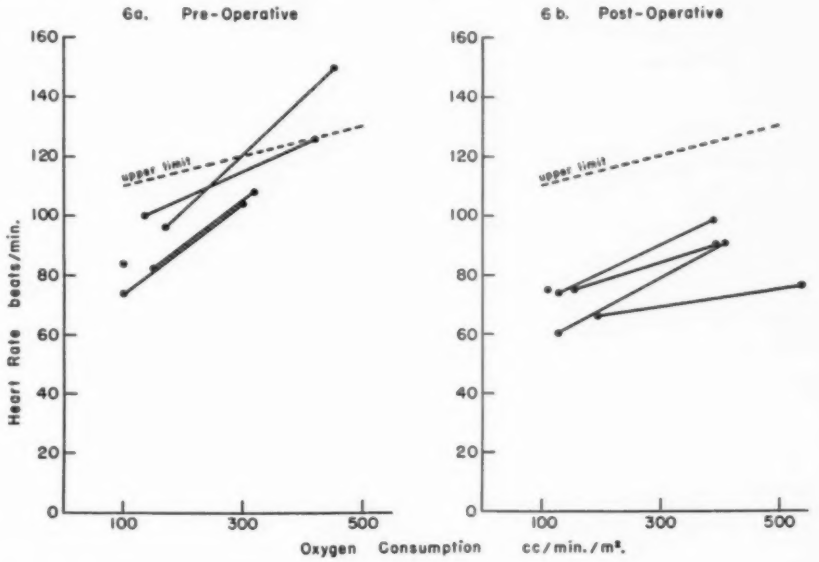

Fig. 6.—Heart rate.

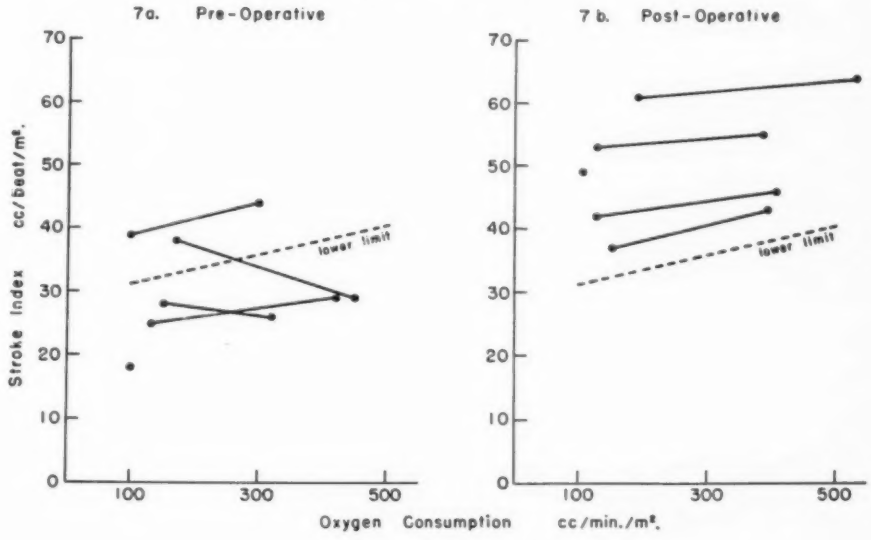

Fig. 7.—Stroke index.

The results concerning cardiac output and stroke volume before operation were in general in harmony with observations made previously by other methods. As is shown in Table I, three of the five patients exhibited diminished stroke index and cardiac index under conditions of rest, while two were within the normal range as defined above. · *In none of the four patients studied preoperatively under*

conditions of exercise was the stroke index significantly increased during the period of increased oxygen consumption. Therefore, the cardiac index, when it increased, did so only in relation to the increase in the heart rate. Four patients were studied after operation and in each of these there was a significant increase in the resting stroke index—an increase of from 12 to 24 c.c. per beat. But the stroke index still did not increase any further when these treated patients were observed during exercise.

The pressure measurements, particularly those in the pulmonary circuit, contribute the new and most significant information resulting from these studies. Before operation the resting pressures in the pulmonary "capillaries," the right ventricle, the right auricle, and the systemic veins were strikingly elevated in every patient. Moreover, these pressures rose further on exercise. After operation the pressures changed toward the normal. In some instances this change toward normal was marked (for example, the resting pulmonary capillary mean pressure fell from 27 to 17 in Patient 1) but in no case was there a complete return to what could be accepted as normal intravascular pressures.

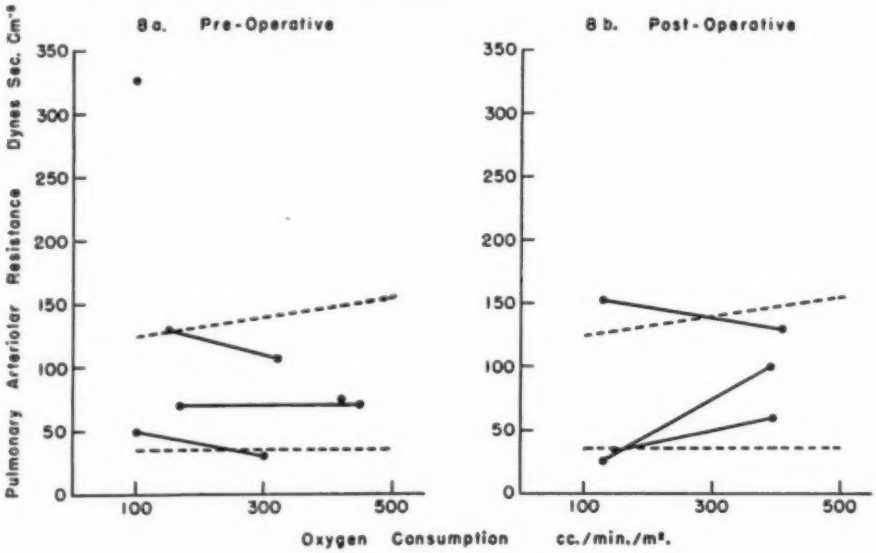

Fig. 8.—Pulmonary arteriolar resistance.

The pulmonary arteriolar and the total peripheral resistances before operation were within the range of normal except in Patient 4, who had an elevated pulmonary arteriolar resistance considered to be due to pulmonary vascular disease associated with emphysema.

The definite but slight changes in circulatory dynamics which followed operation were accompanied in each patient by an impressive improvement in comfort and in capacity for activity.

It will be well at this point to summarize the history of each patient, the operation that was performed, the alterations in dynamics following operation, and the resulting changes in symptoms and activity associated with the changes in dynamics.

CASE REPORTS

CASE 1.—E. L., was a 48-year-old man. Six years before admission he had suffered abdominal and chest pain and disabling weakness. A diagnosis of heart strain was made. For four years before admission he had had increasing edema of the legs, and progressively severe dyspnea. Orthopnea was of recent onset and mild degree. A diagnosis of constrictive pericarditis was made at the Cushing Veterans Administration Hospital and he was transferred to the Peter Bent Brigham Hospital for study and treatment. He showed a normal sized heart, evidence of venous congestion, and a paradoxical pulse. The venous pressure was 270 mm. H O. X-ray examination showed a line of calcium surrounding the cardiac silhouette. Pericardiectomy was advised.

An incision was made 2 cm. anterior to the left phrenic nerve and carried through layer after layer of onion-skin-like fibrous coating until the myocardium herniated through the incision. Dissection between pericardial and epicardial layers was then carried out with freeing of the left border of the left ventricle and entire right ventricle anteriorly. A total area of 12 × 12 cm. of pericardium was removed over the left heart border, apex, and right ventricle. The residual right ventricular pericardium and all pericardium over the left ventricle and posterior to the phrenic nerve were lysed. No auricular decortication was carried out. The inferior vena cava was exposed. One area of pericardium over the circumflex coronary artery, approximately 3 × 5 cm. and containing calcification, was not removed.

Immediately after operation there was a superficial thrombophlebitis of the right leg which responded well to heparin therapy. Ten weeks following operation the patient was able to walk a distance of two city blocks and had only slight swelling of the ankles during the day. He was comfortable when lying flat. One year after operation he was able to climb two flights of stairs; he was ambulatory throughout the day, but he still was unable to work. During the year he had several episodes of chills and fever associated with mild costovertebral pain. These represented acute flare-ups of chronic pyelonephritis, and required appropriate management.

Preoperative catheterization revealed a limited stroke volume and elevated pressure in pulmonary capillary, pulmonary artery (diastolic), right ventricle (end diastolic), right auricle, and peripheral veins. Cardiac catheterization ten weeks following operation showed a higher cardiac output than that observed preoperatively. These postoperative output figures were essentially normal. Pressures were slightly lower than preoperatively. One year following operation the pulmonary capillary pressure was still elevated at rest and rose further on exercise. The pulse pressure in the right ventricle was still narrow, the diastolic pressure at rest was elevated, and both systolic and diastolic pressures rose to abnormally high levels on exercise. This patient thus had moderate improvement in comfort and in range of activity, slight improvement in pressures, and some rise of cardiac output.

CASE 2.—E. P., as an Army truck driver, began at the age of 29 years, to experience an unaccustomed dyspnea and fatigue on exertion. This led to his discharge from the Army. For a time he worked as a truck driver in civilian life, but increasing dyspnea, the development of orthopnea, and finally edema eventually disabled him. At the Cushing Veterans Administration Hospital he was found to have auricular fibrillation, calcification of the pericardium, and a persistently elevated venous pressure. The diagnosis of constrictive pericarditis was made and pericardiectomy was carried out by Dr. Dwight Harken.

Anteriorly, the pericardium was removed from the ventricles as far to the left as the phrenic nerve and to the right beyond the mid-sternal line. A 9 × 12 cm. area of pericardium was removed over the left border of the heart, apex of the left ventricle, and left half of the right ventricle. Pericardial lysis was carried out over the remaining area of the right ventricle and an area of the left ventricle posterior to the phrenic nerve, while the pericardium over the auricles and over the right half of the right ventricle and the posterior half of the left ventricle was left behind.

The immediate postoperative course was uneventful, and the patient was subjectively much better. Thirty-three weeks following operation the patient was restudied. At this time he had no ankle edema, nocturnal dyspnea, or orthopnea. He was able to walk one-half mile without difficulty. Seven months later the patient had no complaints. Several days each week he was helping his brother lay cinder blocks. At this time the venous pressure was 125 mm. of saline.

Cardiac catheterization studies were done preoperatively, and two weeks and thirty-three weeks after operation. Catheterization before operation revealed figures for output and pressures compatible with constrictive pericarditis. Two weeks after operation the stroke index was still decreased although the cardiac index was maintained within the normal range. There was no significant change in the pulmonary capillary and right ventricular diastolic pressures. Thirty-three weeks after operation, stroke index and cardiac index were entirely normal on rest and exercise. The pulmonary capillary pressure was not recorded. The right ventricular systolic and diastolic pressures were slightly elevated at rest. The diastolic pressure rose little on exercise.

This patient showed marked improvement in comfort and activity. He had an equally impressive change in dynamics, which were almost normal thirty-three weeks after operation.

CASE 3.—C. R., a 55-year-old letter carrier, suffered an insidious onset of peripheral congestion in the latter part of 1948. His study at the Cushing Veterans Administration Hospital revealed a persistent elevation of venous pressure, electrocardiographic changes consistent with pericardial involvement, and x-ray evidence of pericardial calcification. The pulse pressure was small and a paradoxical pulse was present. The heart was not enlarged. A diagnosis of constrictive pericarditis was made.

Pericardial dissection was started 1 cm. anterior to the left phrenic nerve. It was with some difficulty that the plane between the innermost pericardium and epicardium was reached, and in some areas the epicardium was removed with the pericardium; 14 × 10 cm. of pericardium were removed over the left half of the right ventricle and left border of the heart including the apex. A large abscess (containing approximately 130 c.c. of pus and having calcific walls) was encountered over the auriculoventricular groove in the area of the left auricular appendage and under the pulmonary artery. Calcification in this wall prevented pericardiectomy or pericardial lysis over the left aspect of the base of the right ventricle and a corresponding area of the left ventricle. Total ventricular pericardial lysis was carried out posterior to the phrenic nerve and as far to the right as the inferior vena cava.

The immediate postoperative course was uneventful except for the rapid accumulation of fluid in the left pleural space. This required numerous thoracenteses. Three months following operation, the patient was ill for two months with serum hepatitis. There was no edema or ascites either before or during this episode. A year after pericardiectomy the patient reported that each day he was feeling better and that he planned to return to work (clerical work at the post office) the next month.

One month postoperatively, as shown in Table I, this patient had normal or almost normal cardiac and stroke indices at rest and exercise, which represented an improvement over the preoperative values. Pressures in the lesser circuit showed no significant change from those present before operation. One year after operation, stroke and cardiac indices were in the limits of low normal. Pressures in the pulmonary artery were normal at rest, but became abnormally elevated on exercise. Right ventricular pulse pressure was narrow, the diastolic pressure being elevated at rest and rising further with exercise. This patient then had had a definite change for the better in both symptoms and dynamics.

CASE 4.—H. C., after many years of good health, suffered the onset of disability at the age of 68 years. Dyspnea was the first symptom. It came on gradually and was soon accompanied by swelling of the feet and legs. When seen he exhibited venous distension, slight cardiac enlargement, and no evidence of valve disease. The blood pressure was 115/84 mm. Hg during normal breathing and 100/80 mm. Hg when the breath was held; the systolic pressure fell 15 mm. Hg with a deep inspiration. The liver was enlarged. There was evidence of chronic pulmonary disease with emphysema. On a low-salt diet, diuretics, and digitalis, he improved somewhat, but the venous pressure was never observed to be normal. Three years after his first visit he was admitted for definitive treatment. Catheterization revealed (see Table I) a slightly elevated pulmonary capillary pressure, a small output per beat, and high pressures in the pulmonary artery, right ventricle, and right atrium. Pericardiectomy was undertaken.

While peeling back the pericardium, a hole was made in the right ventricle, but bleeding was controlled with several sutures. Over the ventricles the dissection was carried as far to the left as the phrenic nerve, but not quite so far to the right. The left ventricle was freed first.

The immediate postoperative course was complicated by poor wound healing. By seven months after operation, edema and dyspnea had completely disappeared. He was quite active about his country place, but he had to move at a slower pace than the normal individual. Three years after operation, he reported that he was continuing to improve and that each month he seemed to gain in strength. At this time he was doing all the work on his small farm. The peripheral venous pressure was 100 mm. of saline.

Cardiac catheterization was done seven months following operation. Stroke indices at rest and exercise were low normal, and cardiac indices were still below normal. Pressures in the right ventricle were essentially the same as before operation. Pulmonary capillary pressure was not recorded. Three years postoperatively, definite improvement was observed. Stroke indices were normal at rest and exercise. The pulse was quite slow at rest. The cardiac index was lower than normal. The pulmonary capillary pressure was normal at rest, but rose above the normal limit on exercise. The diastolic pressure in the right ventricle was about normal, but rose with exercise. This patient has continued to report frequently. He considers himself essentially well but is somewhat limited in range of activity, even for his age of 72 years, and presumably still has abnormal pressures with exercise.

CASE 5.—L. S., a 58-year-old poultry farmer, was admitted to Cushing Veterans Administration Hospital on Feb. 5, 1949, because of the sudden onset of swelling of the lower extremities. He had had a "bronchial condition" since childhood, occurring each winter and characterized by a choking cough. About fourteen months prior to admission, he suddenly developed edema of the lower extremities. This disappeared in a few days to recur again four months later. The recurrence was associated with moderate dyspnea. The swelling persisted until admission and extended to the scrotum and abdomen.

On examination, he exhibited wasting of muscles, distention of neck veins, and edema of the feet. The heart was slightly enlarged, 14 per cent above normal. No calcification was observed. There was no evidence of valvular disease. The blood pressure was 104/85 mm. Hg. The liver was greatly enlarged. The venous pressure was 270 mm. H_2O in the arms and 275 mm. H_2O in the legs. The characteristic picture associated with constrictive pericarditis was observed at the time of venous catheterization. Decortication of the heart was carried out.

The pericardium was incised layer by layer just anterior to the phrenic nerve over the left ventricle until there was bulging of the myocardium. Then with finger and sharp dissection, the pericardium was separated from the myocardium over the left ventricle anterior to the phrenic nerve and also over the anterior half of the right ventricle. This portion of the pericardium was then excised. An area of pericardium (2.5 × 4.0 cm.) was then excised from an area just posterior to the phrenic nerve. This gave further freeing of the left ventricle. It was a very extensive pericardiectomy and left only the pericardium over the right lateral border of the heart and that posteriorly. There was freeing of the pericardium from the epicardium in these areas, although it was not excised. When this was completed, the pericardium was adherent only over the right and left auricles.

Six months after operation this patient was feeling well and doing a moderate amount of gardening and walking. He had no dyspnea or orthopnea. He exhibited minimal ankle edema, and a vital capacity of 1,600 c.c.; he has had no postoperative catheterization but will be studied again.

CASE 6.—G. M. was studied by catheterization in 1945 when he was 45 years old and seven years after an operation for constrictive pericarditis. He had been seen many times previously at the Peter Bent Brigham Hospital and is known to have had tuberculous pleurisy, pericarditis, and peritonitis before 1938. In 1938, after several years of mild but continuous disability due to tamponade, a pericardiectomy was performed. This was followed by marked expansion of his activity tolerance and he has been able to earn a living as a worker in a candy factory. The venous pressure, which before operation was always above normal, has been in the high normal range since Dr. Cutler's pericardiectomy.

At operation the pericardium over the whole anterior surface of the heart was freed down to the phrenic nerve on the left side and over the entire anterior surface of the right ventricle. Over the right ventricle, an area of broken-down, cheesy material was found. It was necessary to remove a hard epicardial scar before freeing of the right ventricle anteriorly was achieved.

Immediately after the operation the suffused look to this patient's face disappeared and the venous pressure was within normal limits. Within a few days, however, the venous pressure rose again and remained at abnormally high levels for some four months. Since then the resting venous pressure has been normal or slightly elevated. He is able to work regularly in a factory and lives a life of satisfactory but slightly limited activity.

This patient was not catheterized before his operation (which took place in 1938). When he was studied by means of the catheter some ten years after operation he showed a moderate elevation of right ventricular diastolic pressure. Both cardiac index and stroke index were normal at rest. Exercise studies were not done. (This patient's earlier course is reported in full by Lyons and Burwell.[9])

In summary it can be said that his operation was followed by improvement in both comfort and dynamics.

DISCUSSION

The changes in dynamics and in the course of events permit certain conclusions concerning the nature of the physiologic aiterations in constrictive pericarditis. These conclusions have to do with the stroke output (and therefore with the total cardiac output) and with the significance of the observations on pressures as they relate to the functions of the two ventricles.

Before operation, each patient studied had a stroke output less than the normal. It is generally accepted that this reduction in stroke volume is the primary dynamic abnormality of constrictive pericarditis.[10,11] It is, therefore, appropriate to discuss the factors that may influence the stroke volume. According to Bainbridge and Menzies,[12] the stroke output is dependent upon three factors: myocardial contractility, the work load of the ventricles, and diastolic filling.

The observations reported in this paper offer no definitive evidence concerning myocardial contractility. It is, of course, known from post-mortem evidence that in constrictive pericarditis myocardial fibers are often atrophic,[13] and that the myocardium may itself be infiltrated by fibrous tissue, presumably a consequence of the original inflammatory process extending from the pericardium. Common sense suggests that the thick pericardial scar itself may interfere with ventricular contraction. It is easy to see that this might be the case if the pericardium were adherent both to the myocardium and to resistant structures in the neighborhood. It would also be true whenever the pericardium is a rigid resistant structure, even if it is not adherent to the myocardium.

The work load of the ventricles has not been estimated in the patients under consideration because of the many theoretical difficulties in choosing an appropriate zero point for pressure calculations.

Available measurements indicate that the limitation of diastolic filling is the major factor in the reduced stroke volume. In general, diastolic filling is influenced by four factors: (1) The diastolic filling pressure; (2) the adequacy of the blood available for venous return; (3) the duration of diastole, and (4) the ability of the ventricle to dilate. These factors may be considered separately.

First, effective diastolic filling pressure is affected by any degree of obstruction to flow. In the patients studied, there was no evidence of such obstruction in the venae cavae, in the right auricle, or in the right ventricle, that is, the pres-

sures in the superior and inferior cavae, in the right auricle, and in the right ventricle in diastole were essentially identical. It can be stated, on the basis of these observations, that there was no physiologic obstruction to filling of the right ventricle in this group of patients with reduced stroke volume. It also can be stated that the filling pressure of the right ventricle as determined by direct measurements was markedly elevated in each patient.

These studies do not offer such direct evidence concerning left ventricular filling since the method used does not permit the measurements of the pressures in the pulmonary veins, the left auricle, or the left ventricle. Obstructions to flow in pulmonary veins or left auricle are theoretically possible, but no evidence has been presented in the literature that physiologic obstruction to flow, as shown by an abnormal pressure gradient, exists in any of these places in patients with constrictive pericarditis. Moreover, the pulmonary capillary pressure contours in each of these patients were similar to pressure contours which are seen in the left auricle,[14] and this is indirect evidence that no obstruction exists between the pulmonary veins and the left auricle. It seems justifiable, therefore, to use pulmonary capillary pressure as an approximation of left ventricular diastolic filling pressure. If this approximation is accepted, it may be said that filling pressure of the left ventricle was markedly elevated in each patient studied and that this filling pressure was essentially of the same magnitude as the filling pressure of the right ventricle in the same patient.

Second, consideration is also to be given to the adequacy of the blood available for venous return. The visible distension of peripheral veins indicated that there was no deficiency in the volume of blood available to the right side of the heart; the evidence of pulmonary engorgement indicated the presence of an increased volume of blood in the vessels of the lung where it was available to the left ventricle.

Third, the duration of diastole of the left ventricle was not shortened in four patients in whom adequate preoperative measurements were made.

Fourth, the degree of ventricular dilatation sets a limit to the stroke output. Physiologic dilatation is a necessary mechanism in the increase of stroke output. Such a dilatation implies an increase in fiber length and a resultant increase in the force of contraction. These mechanisms are obviously impaired by a constricting scar, and the figures presented have emphasized the constancy and severity of this impairment in patients with constrictive pericarditis. Therefore, the evidence indicates that reduced stroke output is the major factor in the disability of this disease. The reduced output is due to the fact that dilatation of the ventricle is limited by the constricting scar.

Cardiac output per minute is the product of stroke output and heart rate. In Case 1 there was a considerable increase of cardiac output on exercise, entirely accounted for by an increased heart rate. The increase of cardiac output in Cases 3 and 5 was likewise attributable to tachycardia. In Case 2, the rate was so rapid that the diastolic filling time was shortened and the stroke index decreased (see Table I). The cardiac index, therefore, was only slightly increased by the tachycardia.

With a low cardiac output, the oxygen supply to the peripheral tissues is maintained by an increased extraction of oxygen from the blood (that is, a wide arteriovenous oxygen difference). The reduced output in these patients is comparable to that seen in pulmonary hypertension,[15-17] left ventricular failure,[18] pulmonic stenosis,[19] and mitral stenosis.[20] It is curious that tachycardia at rest is not a more prominent finding in these patients whose low cardiac output could, at least in some instances, be higher if the pulse were more rapid. Most patients with constrictive pericarditis exhibit a heart rate more rapid than the normal; this group is unusual in this respect. In the twenty-eight patients reported by Burwell and Blalock, rates of 90 to 120 were frequent and some degree of elevation of heart rate was observed in every patient. In the group of six patients here reported the resting heart rates preoperatively were, respectively: 74, 96, 100, 84, 82, and 77. Some of the difference between these groups of patients may be due to a difference in the stage of disease. More than one-half of Burwell and Blalock's[10] patients had active pericardial infection (usually tuberculous) at the time of operation and many had some elevation of temperature. The patients in the present series were older, the constriction had been present for months or years, and active infection was not demonstrated.

The next discussion is concerned with the observations on *intravascular pressures*. Each of these patients exhibited the expected elevation of peripheral venous pressure and this was taken to indicate an abnormal function of the right side of the heart. Pressures in right auricles and right ventricles did not indicate any obstruction to flow from vena cava to auricle, or through the auricle, or from auricle to ventricle. It appears, therefore, that the abnormal function of the right side of the heart may be attributed to less than normal dilatation of the right ventricle and consequent limitation of the stroke volume.

Each patient also exhibited a rise in pulmonary capillary pressure to a level approximating the peripheral venous pressure. This is a new and significant observation. It has been generally held that in patients with constrictive pericarditis the congestion of the lungs is less severe than that of the periphery. The evidence presented here makes it possible to correct that impression and also to explain some of the differences between the pulmonary congestion of constrictive pericarditis and that of mitral stenosis or of failure of the left ventricular muscle. Each of the patients with this type of pericardial disease had a striking elevation of pulmonary capillary pressures, which is considered to reflect pulmonary venous pressure; and in each patient this was approximately equivalent to the right atrial pressure (Table II). Therefore, pulmonary congestion was present, and to about the same degree as peripheral congestion. Other evidence was also available. Four of these six patients had râles at the bases, and some degree of orthopnea, and roentgenograms showed prominent pulmonary vascular markings although these were never extreme. The total evidence of pulmonary congestion is interpreted as indicating involvement of the left ventricle in the constricting scar.

This series of studies also supplies an explanation of the special characteristics of the pulmonary congestion of constrictive pericarditis. It is general experience that severe paroxysmal dyspnea or sudden attacks of pulmonary

edema are rare in these patients. Consider the changes in pulmonary capillary pressures which occur with exercise! All these patients had resting pulmonary capillary pressures of less than 30 mm. Hg. That is, the pressure, while definitely above normal, did not reach the level at which gross edema of the lungs is ordinarily observed. With exercise the pulmonary capillary pressure rose, but in no case to a level greater than 42 mm. Hg, far less of a rise than is seen in a comparable group of patients with left ventricular failure or with mitral stenosis.

The observations here reported seem to indicate that the reason for the rarity of severe or paroxysmal pulmonary edema in constrictive pericarditis is the relative impotence of the right ventricle. When, as in mitral stenosis or left ventricular failure, the right ventricle is relatively competent it can raise the pressures in the pulmonary circuit abruptly and literally flood the lungs with blood. In constrictive pericarditis this is not so; as appears in Table II the right ventricle can bring about only relatively small changes in the degree of pulmonary congestion.

Furthermore, patients with constrictive pericarditis reach the limit of their endurance and stop exercising before gross pulmonary edema has developed. This limited exercise tolerance is presumably a consequence of the low cardiac output.

Further light on the pathologic physiology of this disorder may be sought from the results of operative treatment. In these patients at operation, the heart was seen to dilate as the pericardium was opened. This is, of course, a frequent experience, and acute dilatation with death has, in a few instances,[21] occurred during operation. From the point of view of the present discussion, the importance of this observation is that it shows that the heart has been released from the constricting pericardium to such a degree that dilatation can take place.

However, in spite of this evidence of the immediate effectiveness of operation and in spite of the improved health of many patients after pericardiectomy, it is clear that the simple concept of limited stroke volume due to pericardial constriction is not the whole story. Most patients with this disease are improved by operation, but they are rarely cured. This is borne out by critical observations of series of patients over a period of years and by the fact that, in the group reported in this paper, in no case were the circulatory dynamics entirely normal, even when studied months or years after operation.

What are some of the factors that interfered with the effectiveness of surgical treatment in constrictive pericarditis in these six patients?

First, in none of these patients was decortication of the ventricles complete, although in several it was extensive. The persistence of elevated filling pressures after operation, particularly in relation to the left ventricle, suggests that inadequate release of the left ventricle was a factor. This can be corrected in future operations. Holman and Willett[22] have also recommended a more extensive decortication. However, they consider that excision should be made of scar tissue adherent to auricles and great veins as well as that adherent to the ventricles. They submit no pressure measurements to support this point of view. The measurements in the patients of the present series offer no support to this belief

as to the physiologic importance of the scars involving auricles and veins. These measurements confirm their judgment of the physiologic importance of the scars constricting the ventricles. Obviously excision of scar tissue over auricles and veins must add to the duration and hazard of the operation.

Second, the gradual and progressive improvement over months and years suggests some factor in addition to incomplete resection. An obvious possibility is a change in function of the myocardium itself. Myocardial fibrosis and myocardial atrophy are often encountered at necropsy in these patients. The pattern of circulatory disturbance in patients with diffuse fibrosis of the myocardium without pericardial involvement may mimic to some degree that seen in patients with constrictive pericarditis.

An instructive example may be cited:

W. L. was a 38-year-old streetcar conductor whose past history was entirely noncontributory. In 1945 he first noted shortness of breath on exertion. In 1946 he was hospitalized elsewhere for two months because of influenza (the virus was identified as "A") and pneumonia, in the course of which he was treated with digitalis. Within a few days after discharge from the hospital, he went to another hospital because of marked exertional dyspnea, orthopnea, and abdominal swelling. After six months he was sent home and was able to perform sedentary tasks. Despite digitalization, a low-salt diet, and weekly injections of mercurial diuretics, he was severely incapacitated. At no time did he have chest pain or joint symptoms. Because of the absence of improvement and failure to demonstrate an obvious cause for his cardiac disability, he was referred to the Peter Bent Brigham Hospital for special studies. On physical examination he was pinched and thin. Blood pressure was 115/80 mm. Hg. Veins in the neck were distended and pulsating. The apex impulse was in the anterior axillary line. The rhythm was regular. No murmurs were audible. The pulmonic second sound was accentuated. There were a few basal râles in the lungs and signs of congestion were present bilaterally. Ascites was marked. The liver was enlarged. There was pretibial pitting edema. The hemoglobin, hematocrit, and blood urea nitrogen were normal. The electrocardiogram revealed right axis deviation and changes consistent with myocardial damage. The vital capacity was 1,800 c.c. The circulation time (Decholin) was 35 seconds. X-ray examination revealed a large heart with small excursions. There was prominence of the hilar and intrapulmonary vascular markings.

Cardiac catheterization was carried out at this time as described under Methods, with the following salient findings:

(Body surface area 1.65 sq. M.; anterior-posterior diameter of chest 20 cm.)

FINDINGS	REST
O_2 consumption c. c./min.	189
A-V O_2 difference c.c./L.	75
Cardiac index L./min./sq. M.	1.5
Pulse rate per minute	80
Stroke index c.c./beat/sq. M.	19
Pressures (mm. Hg)	
Pulmonary capillary (mean)	40
Pulmonary artery (systolic/diastolic)	75/42
Right ventricle (systolic/diastolic)	74/40
Right auricle (mean)	40
Venous pressure	38

Three months later, the patient's condition was not improved. Exploration revealed a normal pericardium. Eight months later the patient died of progressive cardiac insufficiency without chest pain at any time. Post-mortem examination revealed gross old occlusions of all

three main coronary arteries by atherosclerosis with multiple occlusions and myocardial infarcts old and new. There was extensive myocardial fibrosis. The pericardium was normal.

The course of this patient's disease was not unlike that frequently seen in constrictive pericarditis. The onset was slow and insidious without obvious etiology. The course was one of progressive disability without periods of remission and relapse. Moreover, in many ways the dynamics were similar to those of constrictive pericarditis. The stroke index was greatly reduced and the pulmonary capillary and right atrial pressures were elevated to about the same degree. The right ventricular pressures (systolic and diastolic) were 74/40 mm. Hg. The right ventricular pulse pressure was therefore 34. In the patients with constrictive pericarditis, comparable figures were: 14, 17, 22, and 11, in the four individuals in whom acceptable measurements were made. Thus, the right ventricular pulse pressure was greater in this patient with myocardial fibrosis than in the patients with pericardial constriction. However, it is also appropriate to consider pulse pressure in relation to the existing level of intravascular pressure, for example, the end-diastolic pressure. If this comparison is made it is found that in both the patient with myocardial fibrosis and three out of four of the patients with constrictive pericarditis, the right ventricular pulse pressure is less than the end-diastolic pressure. Moreover, in none of the five patients with constrictive pericarditis studied preoperatively was the pulmonary artery systolic pressure greater than 40 mm. Hg (Table II), although pressures greater than this are not rare in patients with left ventricular failure or with mitral stenosis.

This experience suggests that, if myocardial fibrosis is extensive, pericardiectomy may not be successful in the treatment of constrictive pericardial disease. No such clear evidence exists in the case of myocardial atrophy but the gradual improvement in symptoms and in dynamics (months or years after operation) suggests a gradual improvement in the function of the myocardium. This in turn suggests that atrophy as well as fibrosis may be a factor.

Certain of the observations reported in this paper have direct therapeutic implications. First, the involvement of the left ventricle in the constricting scar is more severe and more productive of disability than has heretofore been apparent. This observation clarifies the specific objective of operative treatment. This objective is the release of both the right and left ventricles as completely as possible from the constricting scar which limits their diastolic size. The definition of objectives has been debated for years. Schmieden[21] as early as 1926 stated that decortication of the left ventricle was the most important part of the procedure. Burwell[10] and Blalock on the basis of their observations believed that major emphasis should be placed on decorticating the right ventricle but that both ventricles should be freed. They discouraged attempts to remove scar tissue from about the venae cavae as they considered this dangerous and unnecessary. Churchill[24] stressed the importance of freeing the right auriculoventricular groove. Holman and Willett[22] have reviewed the various proposals and added their own. They recommend that all surfaces of the heart be liberated and they believe it important to free the two venae cavae as well.

A recent report[25] by White, Alexander, Churchill, and Sweet deals with three patients who required multiple operations because of inadequate release of the left ventricle and supports the concept of the importance of the involvement of this chamber. Another striking example is the patient reported by Hitzig.[26] This woman patient had recurrent ascites requiring 150 paracenteses over a period of nine years. A block of the inferior vena cava was postulated (although no differential pressures were recorded) and the initial operation was directed at freeing this vessel and the right ventricle. There was no improvement. Six months later the left ventricle was decorticated and this procedure was followed by striking improvement.

Thus, both experience and the critical measurements reported in this paper point to the necessity of releasing both ventricles, left as well as right. No such clear evidence supports the position that the scars surrounding auricles and great veins have comparable significance. It is true that from time to time the surgeon or the pathologist encounters a visible localized anatomic constriction in the venae cavae or in the groove between right auricle and right ventricle.[22,27] However, it has not been demonstrated that such constrictions are physiologically significant. In the patients reported in Table II there is no abnormal fall of pressure between vein and right auricle or right auricle and ventricle to indicate such an obstruction on the right side of the heart. Similar data are not available for the left side of the heart but it is believed that the pulmonary capillary pressure tracing is significant. In the patients here reported a good auricular pressure pattern was seen. It was accordingly concluded that there was no significant pulmonary vein obstruction.

Therefore, in so far as these six patients are representative of constrictive pericarditis, the objectives of surgery appear to be the decortication and release of the two ventricles. Such an operative procedure constitutes the definitive therapy of constrictive pericarditis. Demonstration of the importance of myocardial involvement raises the further question of whether atrophy, residual inflammation, and fibrosis can be prevented or modified.

The usual cause of constrictive pericarditis is tuberculosis.[10,28] When the original acute pericarditis is recognizable it is now possible to use antibiotics in an attempt to control or ameliorate the inflammatory process. Antibiotic treatment may also permit definitive surgery earlier in the course of disease than would otherwise be advisable. This early operation would tend to reduce myocardial atrophy; both antibiotics and earlier operation should help minimize myocardial fibrosis.

SUMMARY

1. The methods of catheterization of the heart and the pulmonary vessels make it practical, for the first time, to investigate the pressure and flow phenomena in the right side of the heart and in the pulmonary vascular system of patients with constrictive pericarditis. Six such patients have been studied by these methods.

2. Every patient showed an elevation of pulmonary "capillary" pressure (which reflects pulmonary venous pressure). This demonstration of pulmonary congestion is interpreted as indicating that involvement of the left ventricle plays a more important and sinister role in the functional changes associated with pericardial constriction than has been demonstrated previously.

3. Every patient also showed an elevation of pressure in peripheral veins and in right atrium, and pressure measurements in the right ventricle and pulmonary artery which indicate a reduced ability of the right ventricle to contribute to the forward movement of blood. These observations confirm and emphasize the previously recognized involvement of the right ventricle.

4. In every patient before operation the mean pulmonary capillary pressure was approximately equal to the peripheral venous pressure.

5. No patient exhibited pressure changes pointing to physiologically significant obstruction in great veins or auricles.

6. The limitation of stroke volume and cardiac output per minute in constrictive pericarditis previously demonstrated by other methods is confirmed by these studies.

7. Consideration of the course of events after operation suggests that myocardial atrophy, myocardial fibrosis, and incomplete release of the ventricles may all play a role in the slow, and in most cases, incomplete return to normal dynamics after operation.

8. The specific therapeutic implications of this study are: (A) the objective of surgery is the adequate release of both ventricles; (B) no indications have been found for the decortication of great veins or auricles, and (C) the early use of antibiotics in acute tuberculous pericarditis may minimize myocardial fibrosis and may permit operative treatment before myocardial atrophy is severe.

9. Finally, the fact that improvement after operation is often slow and often incomplete in terms of objective measurement should not lead physicians to ignore the more important fact that a well-planned operation for constrictive pericarditis has in the past usually made the difference between invalidism and activity. The studies reported in this paper may be expected to make future operations for this disorder even more effective.

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STUDIES ON THE MECHANISM OF VENTRICULAR ACTIVITY

III. Contraction of the Ventricles in Experimental Bundle Branch Block

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THE EARLY confusion that existed in the terminology of right and left bundle branch block is a well-known phase of the history of this disorder. Perhaps the most important single contribution toward the clarification of this confusion was Wilson and associates' demonstration in 1932[1] that, in cases of bundle branch block, the intrinsicoid deflection is recorded late in chest leads taken over the involved ventricle. This fact has received widespread acceptance and now comprises the principal basis for the designation of bundle branch block as being of the right or left type. Although the question of asynchronous ventricular contraction in bundle branch block has been extensively studied, universal agreement on its existence has not been achieved.

In the effort to determine the presence or absence of the expected type of ventricular asynchrony which would correspond to the existing bundle branch lesion, various pulse or pressure recordings have been used in conjunction with the electrocardiogram or other pressure curves. From most but not all of these investigations it was concluded that asynchrony of the expected type had been demonstrated to occur in bundle branch block. With but few exceptions, these studies were based upon measurements of the interval between some portion of the QRS complex and the registration of a pulse or pressure phenomenon. The reliability of such "electro-mechanical" intervals for accurate time measurements has been questioned,[2,3a] and more recently, in a large series of patients with bundle branch block carefully studied by dual-channel electrokymography, it was impossible to find significant correlation between the type of bundle branch block and the type of ventricular asynchrony.[3, a and b] While all pulse registration methods may be subjected to criticism on the basis that they represent more or less indirect methods for studying ventricular contractions, recent information concerning time artifacts associated with the electrokymograph indicate that this instrument is at present unsuited for the study of pulse-time relationships.[4,5]

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Since there is not complete agreement on the subject of ventricular asynchrony in bundle branch block, it seemed desirable to study the problem experimentally, utilizing high-speed cinematography as a method for obtaining direct and unequivocal results.

METHODS

Each of the twelve animals studied was premedicated with morphine sulfate (2.5 mg./kg. of body weight, intramuscularly), and anesthetized with a 25 per cent solution of urethane (approximately 2.5 c.c./kg., intravenously). The chest was opened by a transverse, sternum-splitting procedure, and positive pressure respiration was started. Slow-motion cinematographs (500 to 5,000 frames per second) were made of the beating heart and simultaneously recorded ventricular lead electrocardiograms, before and after severing either the right or left bundle branch. Details of the arrangement which permits photography of the heart and the electrocardiogram as it is being written have been described completely in a recent publication.[6] Bundle branch block was produced by introducing an iridectomy knife through an auricular purse-string suture and placing a transverse cut on the ventricular septum as described by Lewis.[7] Successful experiments were completed in six instances of right bundle branch block, and in six instances of left bundle branch block.

RESULTS

Before describing the abnormal ventricular mechanism, it is necessary to consider briefly the normally beating ventricles. While analysis of the rapid ventricular motions is quite impossible by simple inspection of the beating heart, high-speed cinematographs which slow the motions of the heart many times are well suited for studying these rapid phenomena. With the pericardium removed, the motions of the heart as a whole are much less restricted and appear to be accounted for principally by the left ventricle which comprises the larger muscle mass. The distinctive motions of the right ventricle are readily discernible, although they contribute little to the gross motion of the heart.

An analysis of cinematographs recorded at high speeds and projected at normal speed (16 frames per second) demonstrates that beginning with auricular systole a "bolus" of blood is injected into the right ventricle. This has been referred to in previous publications as the inflow tract[6] and is marked by a wavelike dilatation of the right ventricle proceeding from the atrioventricular groove and approaching the apex and septal attachment of the right ventricle. At almost the same instant that this inflow tract reaches the lower boundaries of the right ventricle, the first signs of ventricular activity appear in the region of the septal junction with the right apex. Contraction rapidly sets in over the free wall of the right ventricle and the "bolus" of blood now forming the outflow tract is propelled wavelike toward the pulmonary conus which contracts somewhat later than the right apex.

As the outflow tract is developing on the right, the first activity of the left ventricle becomes apparent. The motion of the left ventricle is more vigorous

and complicated than the right, and resembles that observed in high-speed cinematographs of the human left ventricle obtained at operation.[8] At the onset of left ventricular activity, there is an anterior thrust of the apex which is accompanied by shortening of the left ventricle on its long axis. Almost immediately there follows a counterclockwise,* twisting, and wringing motion involving the entire left ventricle, but being most evident at the left apex. These forces continue to develop, reaching a maximum just before the onset of diastole.

For purposes of establishing time relationships of the two ventricles as shown in the films, comparison of systole in the pulmonary conus with shortening of the left ventricle on its long axis and elevation of the left apex proved the most satisfactory under the conditions of our experiments. In the control observations these two events occur almost simultaneously (Fig. 1). During right bundle branch block, however, it was found in each instance that the onset of systole in the pulmonary conus is greatly delayed and does not occur until shortening of the left ventricular long axis and elevation of the apex are well developed (Fig. 2). In left bundle branch block, the reverse was found to be true; systole in the region of the pulmonary conus takes place before any evidence of left ventricular activity is apparent. In both right and left bundle branch block, diastole as well as systole in the normal ventricle could be seen to precede these same events on the blocked side by a significant interval.

In instances in which incomplete block was obtained, only slight delay in the onset of ventricular contraction was noted on the side of lesion. However, with the production of a more complete degree of block by additional trauma to the bundle branch, this delay could be greatly increased. Although no precise time measurements could be made, the degree of mechanical asynchrony seemed to vary directly with the degree of electrical asynchrony indicated by the simultaneously recorded right and left ventricular electrocardiographic leads.

DISCUSSION

In the present study, it was found that asynchrony of the expected type occurred between right and left ventricular contractions following experimentally produced bundle branch block. Thus, direct observation of right and left ventricular contraction by means of high-speed cinematography tends to support earlier conclusions based on less direct evidence provided by pulse or pressure recordings registered with other pressure phenomena or an electrocardiogram.[9-16] Although conflicting findings have been reported in some studies employing electrokymographic pulse techniques,[3, a and b] evidence now available indicates that these may have resulted from introduction of time artifacts associated with the electronic equipment.[4,5] With these and other pulse recording techniques, extremely variable results have been obtained in studying asynchrony associated with ventricular extrasystoles. The advantages offered by the directness of the cinematographic technique are to some extent indicated by the fact that the ex-

*When viewed from the apex.

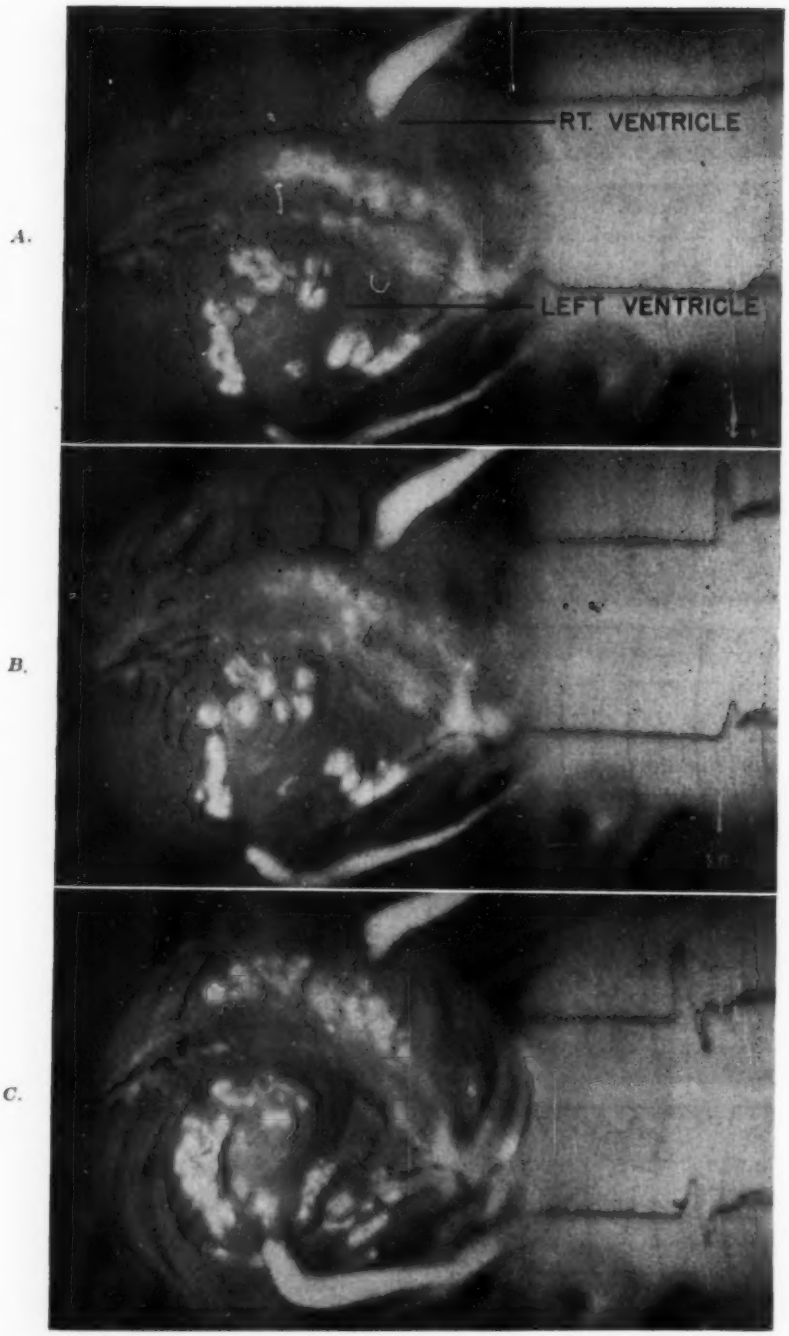

Fig. 1.—Single-frame prints from high-speed cinematographs (2,000 frames per second) of the normal dog's heart and electrocardiogram. The upper tracing is recorded from the cotton electrode on the mid-portion of the right ventricle. The lower tracing is recorded from the electrode on the left ventricular apex. Electrocardiographic paper speed is such that one large square equals 0.04 second. The photographs have been retouched slightly to accentuate the contracting areas.

***A*, Full diastole.**

***B*, Approximately 0.028 second later than *A*. Developing systole is evident in both ventricles.**

***C*, Approximately 0.068 second later than *A*. Near-maximum systole is evident in both ventricles.**

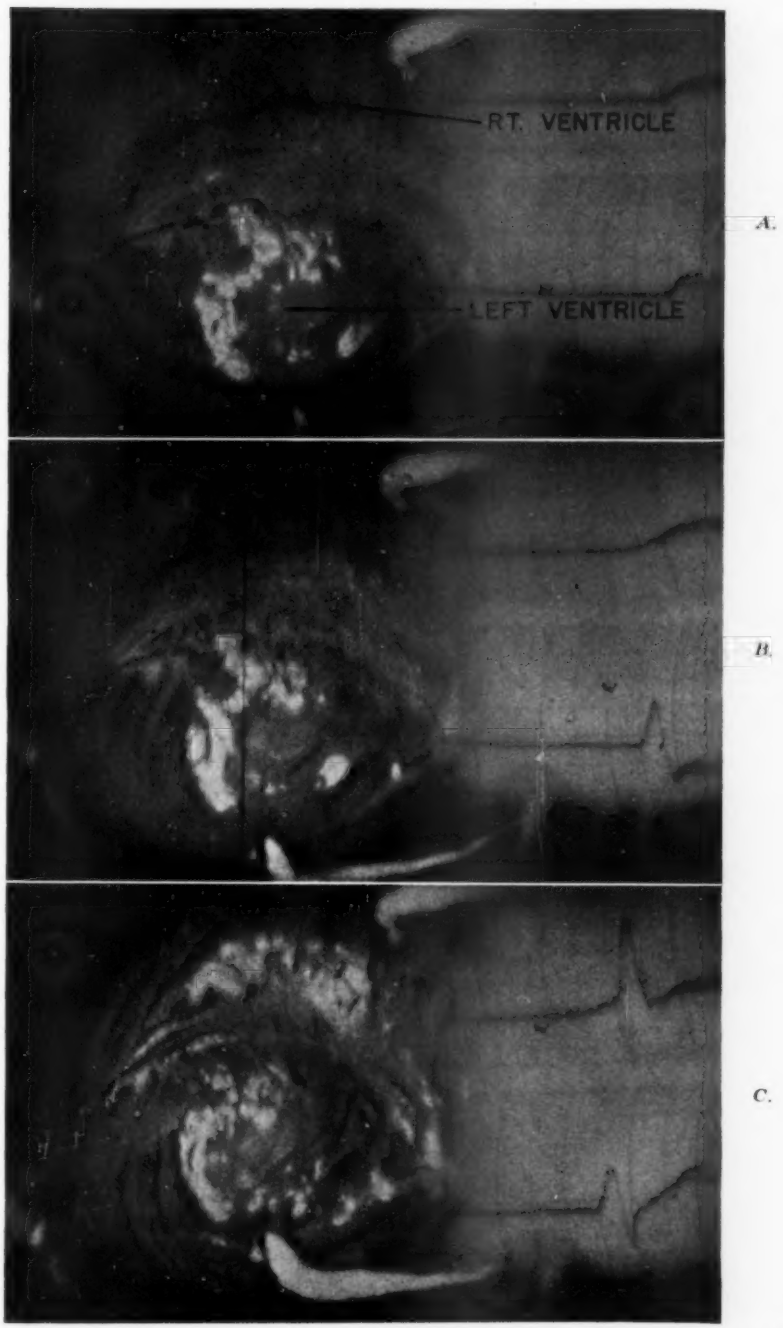

Fig. 2.—Same heart as shown in Fig. 1, following the production of right bundle branch block.

A, Full diastole.

B, Approximately 0.032 second following *A*. Right ventricle is still in full diastole while developing systole is clearly evident on a large portion of the left ventricle. Note that electrical asynchrony is also evident in the electrocardiograms.

C, Approximately 0.096 second later than *A*. Right ventricle is in mid-systole, while the left ventricle has already attained maximum systole.

pected type of asynchrony has been observed to take place consistently in all types of experimentally produced extrasystoles.[8]

In the present study, time measurements of right and left ventricular events were attempted by means of printed, single frame analysis of the films, utilizing the electrocardiographic portion of the frame for a timing reference. However, because of the general character of the heart's motion, measurements by this technique were not sufficiently reproducible to make them quantitatively accurate. Nevertheless, by a comparison of the pre- and post-block films, it was possible to establish the existence of a close relationship between mechanical and electrical events, similar to that proposed by Eyster and associates.[17,18]

SUMMARY AND CONCLUSIONS

High-speed cinematography was employed as a direct method for studying the nature of the ventricular contractions of the dog's heart before and after the production of bundle branch block. During the control observations, the onset of contraction in both ventricles was almost simultaneous. Following the production of bundle branch block, it was found that the onset of ventricular contraction on the side of the lesion was considerably delayed—being most marked in those animals considered to have complete block and being less marked in those having incomplete blocks.

Observations based on analysis of ventricular motion and simultaneously photographed direct electrocardiographic leads from both ventricles support the conclusion that, in bundle branch block, the mechanical and electrical activities on the side of the lesion experience a similar time delay.

The authors wish to express their thanks to Mr. Lou Fields for his technical assistance in the photographic and electronic aspects of this study.

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DISSOCIATION WITH INTERFERENCE IN THE PRESENCE OF 2:1 ATRIOVENTRICULAR BLOCK

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DISSOCIATION with interference occurs when (1) an independent ventricular rhythm develops that is faster than the atrial rhythm, and (2) unidirectional block prevents the excitations of the automatic ventricular rhythm from traveling to the atria and abolishing the sinus rhythm, whereas atrial impulses are able to reach the ventricles.[1]

Occasionally, however, dissociation with interference is present although the automatic ventricular action is slower than the sinus rhythm. This happens when there is 2:1 atrioventricular block, and therefore the rhythm of the conductible atrial impulses is actually slower than the automatic ventricular rhythm. Although arrhythmias of this kind are well defined and present characteristic diagnostic features, few cases have been reported in the literature with correct interpretation of the disorder.[1-5] The condition is often erroneously diagnosed as complete atrioventricular block, or "almost complete block," that is, alternating occurrence of complete and partial block in the same record.

The following two cases, which are the object of this report, seem particularly suitable for presentation of this interesting arrhythmia, because analysis of the underlying mechanism is facilitated by the fact that the ventricular complexes of the conducted beats differ grossly in shape from the automatic ventricular beats.

CASE REPORT

CASE 1.—G. P. W., a 61-year-old man, complained of dizziness and temporary slowing of his heart beat. Hypertensive arteriosclerotic cardiovascular disease was diagnosed. On two examinations, May 21, 1948, and March 3, 1951, sinus rhythm with normal atrioventricular conduction was observed. On Oct. 4, 1949, complete atrioventricular dissociation alternated with normal sinus rhythm.

When the patient was examined on July 28, 1950, auscultation revealed bradycardia and cardiac irregularities. An electrocardiogram taken at that time, (Fig. 1,*A*) shows in Lead I what appears to be complete atrioventricular dissociation. However, the regular ventricular action is interrupted by the premature third ventricular beat which follows a P wave after an interval of 0.16 second. The QRS complex of the premature systole is somewhat different from that of the other beats. Fig. 1,*B* shows three strips of Lead II which form a continuous record. The length of the atrial cycle varies from 0.82 to 0.94 second. The ventricular rhythm is mostly regular, its period ranges from 1.60 to 1.64 seconds. There is obviously atrioventricular disso-

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ciation. However, three ventricular beats (R_4, R_{12}, and R_{18}) occur prematurely after an interval of 1.36 to 1.37 seconds. They are preceded by P waves at an interval of 0.16 second. This suggests that the premature beats are due to sinoauricular excitations which are conducted to the ventricles. The conducted beats differ grossly in shape from the ventricular complexes of the automatic ventricular rhythm.

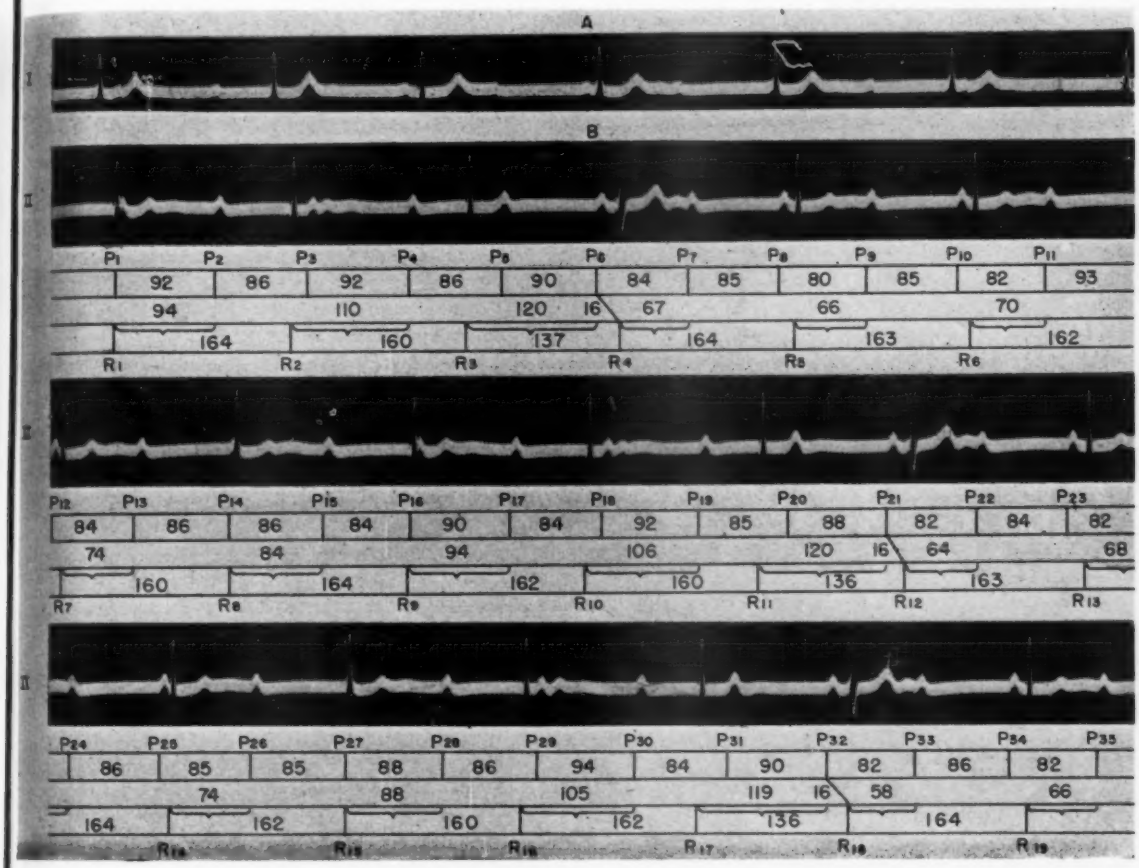


Fig. 1 (Case 1).—*A*, Lead I shows atrioventricular dissociation. The third ventricular beat is premature and its QRS complex differs slightly from that of the other regular beats. The P wave precedes the premature beat at an interval of 0.16 second.

B, Three strips of Lead II form a continuous tracing. There is again atrioventricular dissociation with regular ventricular action which, however, on three occasions is interrupted by premature beats (R_4, R_{12}, and R_{18}). The latter are preceded by a P wave at an interval of 0.16 second. The premature ventricular beats differ in shape from the regular beats; they are obviously conducted from the atria. The conducted atrial excitations (P_6, P_{21}, and P_{32}) fall late in diastole. Their interval from the preceding automatic ventricular beat measures 1.19 to 1.20 seconds, and is conspicuously longer than the sinus period. (The figures in the diagram of this and the following illustrations indicate 1/100 second.)

The atrial impulses which are conducted to the ventricles (P_6, P_{21}, and P_{32}) occur 1.19 to 1.20 seconds after an automatic ventricular beat. The other atrial excitations which fall earlier in the diastole are blocked. Some atrial impulses (P_8, P_{10}, P_{12}, P_{14}, P_{23}, P_{25}, P_{27}, and P_{34}) arrive late enough in diastole to be conducted but are unable to activate the ventricles because they coincide with, or are soon followed by, ventricular escapes.

Thus, atrioventricular dissociation is combined with occasional conducted beats. The arrhythmia differs from ordinary dissociation with interference in two respects: (1) the inde-

pendent ventricular rhythm is slower than the sinus rhythm, and (2) atrial excitations which fall at a time when the refractory period of the bundle is normally terminated are not conducted to the ventricles. Hence, there is atrioventricular block. It appears that conduction of the atrial excitations depends on their distance from the preceding automatic ventricular beat. Since only those atrial impulses are conducted to the ventricles, whose R-P interval is longer than one sinus period, it may be assumed that the basic disorder is a 2:1 atrioventricular block, which is masked by the appearance of ventricular escapes. The validity of this assumption is proved by the observation that occasionally the ventricular escapes disappear and dissociation with interference gives way to undisturbed half rhythm.

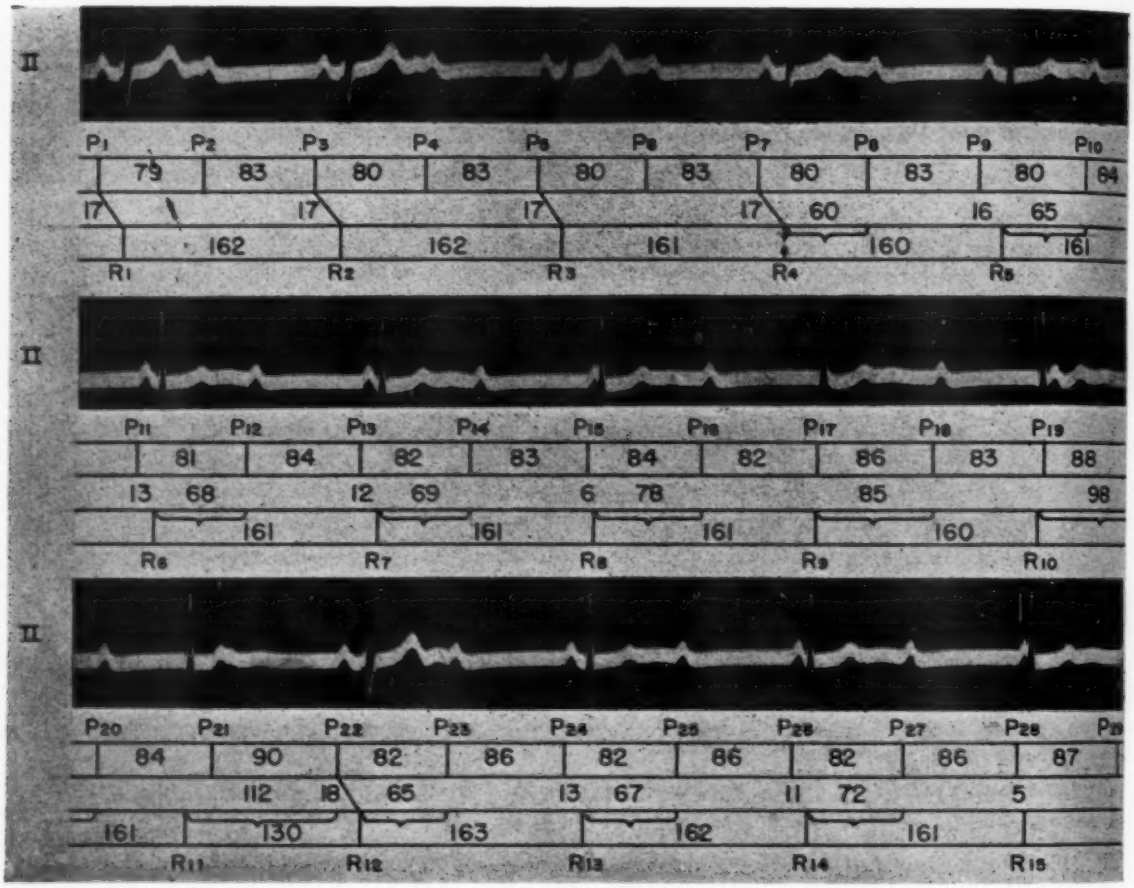


Fig. 2 (Case 1).—Three strips of Lead II form a continuous tracing. The first three beats of the upper strip represent undisturbed 2:1 atrioventricular block. Then, between P_7 and P_{21}, atrioventricular dissociation follows. During the period of dissociation the ventricular beats differ in shape from the conducted ventricular beats (R_1-R_3). R_4 is a ventricular fusion beat. Atrioventricular dissociation is interrupted at P_{22}, which falls 1.12 seconds after the automatic ventricular beat and is conducted to the ventricles after an interval of 0.18 second.

Fig. 2 shows three strips of Lead II, which form a continuous record and are part of one long tracing, the same which included also the pieces shown in Fig. 1. In the upper row of the tracing, the last three beats of a long series of sinoauricular beats are shown, which are conducted to the ventricle at the ratio of 2:1. After P_6 the half rhythm changes to dissociation with interference, apparently because of slight slowing of the atrial rhythm which allows the automatic ventricular center to escape. In this case, the rate of the independent ventricular rhythm differs but slightly from that of the sinoauricular half rhythm, so that a minor acceleration or slowing of either rhythm can readily bring about a change from dissociation with interference to atrial half rhythm and vice

versa. In the first part of the tracing (Fig. 2) the double atrial cycle measures 1.62 seconds and has the same duration as the automatic ventricular period. As long as the atrial impulses are discharged sufficiently in advance of the automatic ventricular stimuli,[2] the sinus rhythm remains in control of the heart (between P_1 and P_6). Then, a slight increase in the length of the atrial cycle, from an average of 0.81 to an average of 0.84 second, allows the ventricular center to escape. Atrioventricular dissociation is established between P_7 and P_{21}. During this period the atrial impulses come either too early in diastole, before the refractory period of the bundle has ended, or they fall too late, either coinciding with, or but slightly preceding, the ventricular escapes. Only P_{22}, which follows R_{11} at an interval of 1.12 seconds, is conducted to the ventricles. The conducted sinoauricular beats, R_{12} as well as R_1 to R_3, differ in the shape of the ventricular complexes from the automatic ventricular beats. R_4 presents an intermediate form between the two types of ventricular complexes, suggesting that the atrial and ventricular centers acting in rapid succession were each able to activate part of the ventricles. Obviously, this would not be possible if the automatic ventricular focus were situated above the bifurcation of the bundle, since such site would preclude the two excitations, using the same pathway, from reaching the ventricles in rapid sequence and producing a ventricular fusion beat.

When the patient was examined last, on March 23, 1951, regular sinus rhythm without atrioventricular conduction disturbance was present. It can be noted, from the tracing taken at that time (Fig. 3), that the ventricular complexes are identical in shape with those of the conducted sinoauricular beats shown in Figs. 1 and 2.

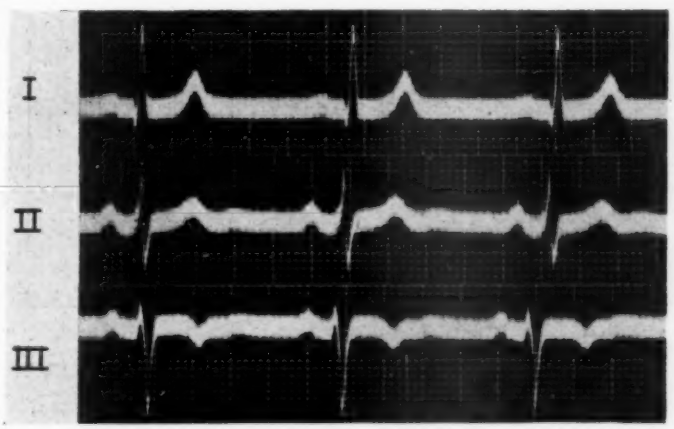


Fig. 3 (Case 1).—Regular sinus rhythm with normal atrioventricular conduction. The shape of the ventricular complex is identical with that of the conducted beats in Figs. 1 and 2.

CASE 2.—A. D., a 68-year-old man, was admitted to the hospital on Oct. 5, 1951, because of attacks of substernal pain and marked dyspnea. Hypertensive arteriosclerotic heart disease was diagnosed. Congestive heart failure necessitated digitalization and periodic administration of mercurial diuretics. Marked bradycardia and irregularity of the heart rhythm were accidental findings which had not been suggested by the patient's complaints.

An electrocardiogram taken on Oct. 6, 1951 (Fig. 4), shows regular sinus rhythm with 2:1 atrioventricular block. The shape of the ventricular complex suggests the presence of left bundle branch block. Another tracing, taken on Oct. 10, 1951 (Fig. 5), shows a fairly regular bradycardia at a rate of 30 per minute. Most of the ventricular complexes have no fixed time relation to P waves; hence, there is atrioventricular dissociation. Two premature beats are noted (R_5 and R_{11}), which are different in shape and resemble the conducted sinoauricular beats of Fig. 4 (Lead II). They follow P waves at an interval of 0.17 second. Obviously, the atrial excitations P_9 and P_{20}, which fall late in diastole, are conducted to the ventricles. Their R-P interval measures 1.55 and 1.46 seconds, respectively, and is conspicuously longer than the sinus period. This suggests that there is 2:1 atrioventricular block. All those atrial waves whose distance from the

automatic ventricular beat is less than 1.46 seconds are blocked. The automatic ventricular rhythm is slower than the sinus rhythm, but is faster than the conductible atrial half rhythm. All these features are characteristic of dissociation with interference in the presence of 2:1 atrioventricular block.

The ventricular cycle that follows the conducted sinoauricular beats is somewhat longer than the average automatic ventricular cycle. R_5 to R_6 measures 2.06 seconds, R_{11} to R_{12} is 2.04 seconds, whereas the length of the automatic ventricular cycle ranges from 1.89 to 1.96 seconds. The prolongation of the ventricular cycle after the premature beat is probably due to the fact that the sinus impulse, in passing to the ventricles, discharges prematurely the automatic ventricular center and exerts an inhibiting effect on the latter. This allows another atrial impulse (P_{11}) to be conducted to the ventricles and to activate part of it, while, in the meantime, the rest of the ventricle has been excited by the delayed automatic ventricular impulse. R_6 is therefore a ventricular fusion beat.

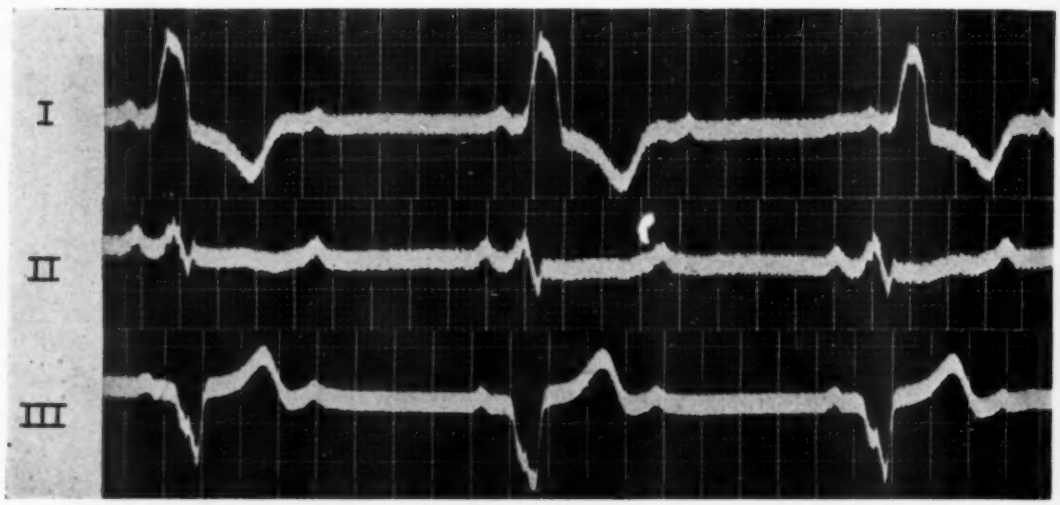


Fig. 4 (Case 2).—There is 2:1 atrioventricular block. The form of the ventricular complexes suggests left bundle branch block.

Occasionally a single conducted atrial impulse, by inhibiting the ventricular pacemaker, may initiate a series of conducted sinoauricular beats. Fig. 6 shows atrioventricular dissociation in the first half of the tracing; the ventricular complexes present features consistent with either right bundle branch block or origin of the excitation in the left ventricle. P_3 and P_5, arriving after an R-P interval of 0.95 and 0.99 seconds, respectively, are blocked. P_7, which follows an automatic ventricular beat at an interval of 1.03 seconds, is conducted to the ventricle with a P-R interval of 0.18 second. Transmission of P_7 causes temporary inhibition of the automatic ventricular center and thus initiates a series of conducted ventricular beats. These show clearly that 2:1 atrioventricular block is present. The ventricular complexes of the conducted beats, like the sinoauricular beats of Fig. 4, present the features of left bundle branch block.

COMMENT

Complete atrioventricular block is usually associated with a regular ventricular rhythm. Gross irregularity of the ventricular action is sometimes observed in advanced stages of coronary artery sclerosis producing an ischemia of the idioventricular pacemaker, and in cases with Adams-Stokes attacks. In some instances of atrioventricular block with dissociated action of atria and ventricles, however, the regular sequence of ventricular beats is periodically interrupted by

shorter ventricular cycles. The ventricular complexes concluding these cycles may or may not differ in shape from the regular ventricular beats. The premature beats show a fixed time relation to a preceding P wave. This suggests that some of the sinoauricular impulses are conducted to the ventricles. The combination of atrioventricular dissociation with periodically conducted sinoauricular beats is suggestive of dissociation with interference. When the automatic ventricular cycle is longer than one sinus period, but shorter than the double atrial cycle, dissociation with interference in the presence of 2:1 atrioventricular block should be considered.

In the presence of this disorder, the conducted atrial impulses show a definite relationship to the preceding automatic ventricular beats. Only those atrial excitations are conducted to the ventricles which fall late in diastole; their R-P interval is close to, and mostly longer than, one sinus cycle. Earlier arriving atrial stimuli are blocked. There is a certain "critical" R-P interval which separates the blocked from the conducted sinoauricular impulses.

Table I compares the R-P intervals of twenty-five conducted and 102 blocked atrial excitations, calculated from one long tracing of Case 1. The abscissae measure the R-P intervals. The dots indicate blocked atrial excitations; the crosses, conducted sinoauricular beats. It can be noted that the R-P intervals of the blocked atrial impulses range from 0.58 to 1.16 seconds, those of the conducted beats from 1.10 to 1.37 seconds. Thus, a clear relationship is demonstrated between atrioventricular conduction and the time of incidence of atrial impulses after an automatic ventricular beat. It is assumed that the excitation of the automatic ventricular center passes the whole or part of the bundle and renders it refractory.[6] Only those atrial impulses are conducted which come late after an automatic ventricular beat. The refractory period of the bundle is indicated by the shortest ("critical") R-P interval of the conducted beats. In the case demonstrated in Table I, the critical R-P interval is close to 1.10 seconds, that is, conspicuously longer than an atrial cycle which, at its maximum, measures 0.94 second (in Figs. 1 and 2). Only six of the blocked atrial impulses have an R-P interval equal to, or slightly longer than 1.10 seconds. This slight overlapping of the R-P ranges of blocked and conducted atrial impulses may be explained by spontaneous variations in the length of the refractory period of the bundle which are known to occur in many clinical cases of atrioventricular block.

Some atrial impulses fall sufficiently late in diastole, after the bundle has recovered its conductivity, but they find their way blocked by ventricular escapes. Under unfavorable conditions no conduction can take place at all, when, namely, the critical R-P interval plus atrioventricular conduction time is longer than the cycle of the automatic ventricular rhythm. Thus, second-degree atrioventricular block may manifest itself as complete atrioventricular dissociation,[2,3] which is readily mistaken for complete atrioventricular block. This happens especially in the presence of higher degrees of partial atrioventricular block. However, spontaneous or drug-produced variations in the rate of the atrial or ventricular rhythm, or in the length of the refractory period of the bundle, often bring about a change from complete atrioventricular dissociation to either dissociation with interference or uncomplicated second-degree atrioventricular block.

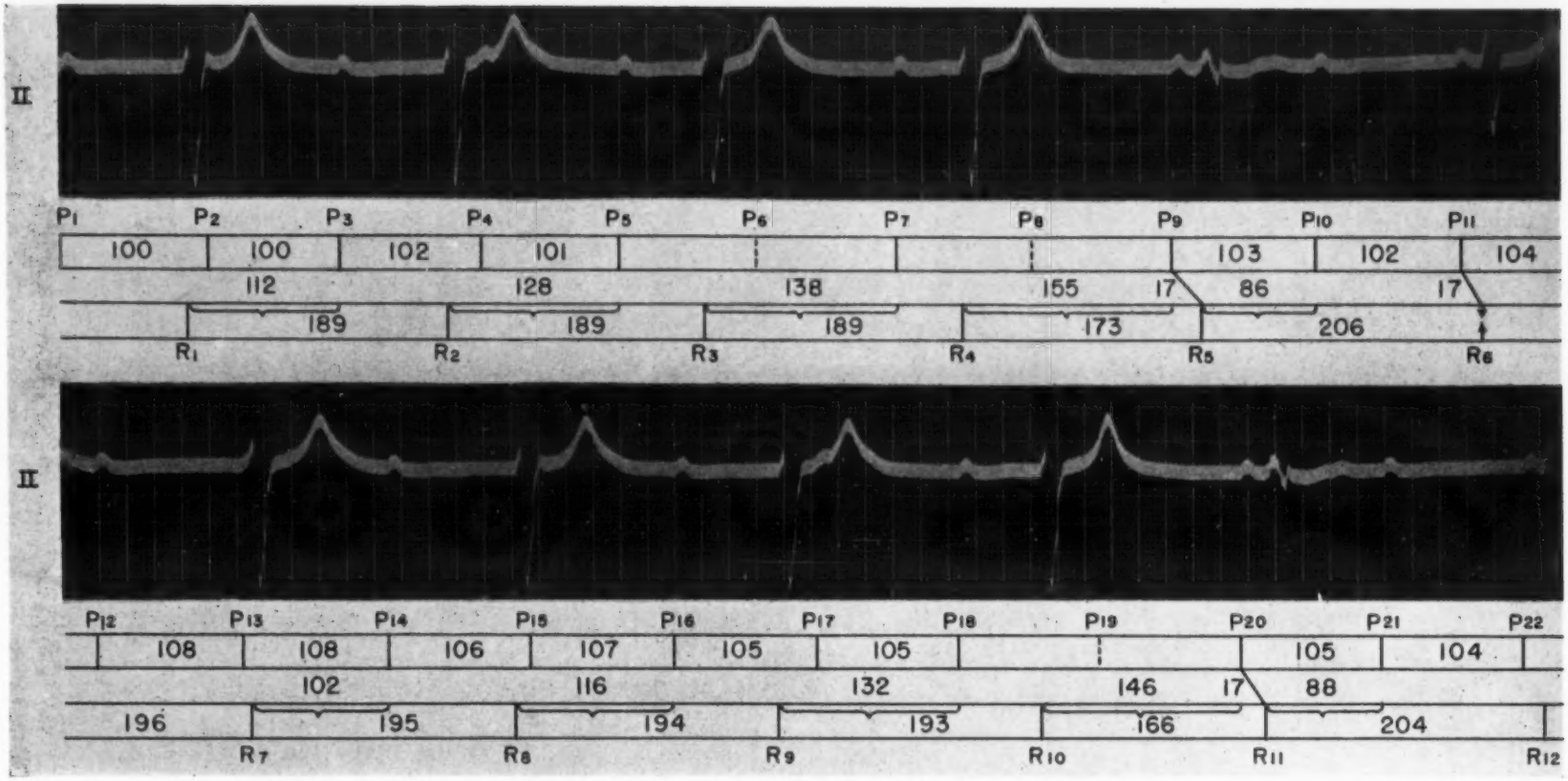


Fig. 5 (Case 2).—Two strips of Lead II form a continuous tracing. The predominating regular ventricular rhythm shows atrioventricular dissociation; it is interrupted twice by slightly premature beats (R_5 and R_{11}). The ventricular complexes of the latter show identical shape with those of the conducted beats in Fig. 4. They are preceded by a P wave at an interval of 0.17 second. These are obviously conducted sinoauricular beats. P_9 and P_{20} fall late in diastole; their R-P interval measures 1.55 and 1.46 seconds, respectively, that is, considerably more than the atrial cycle.

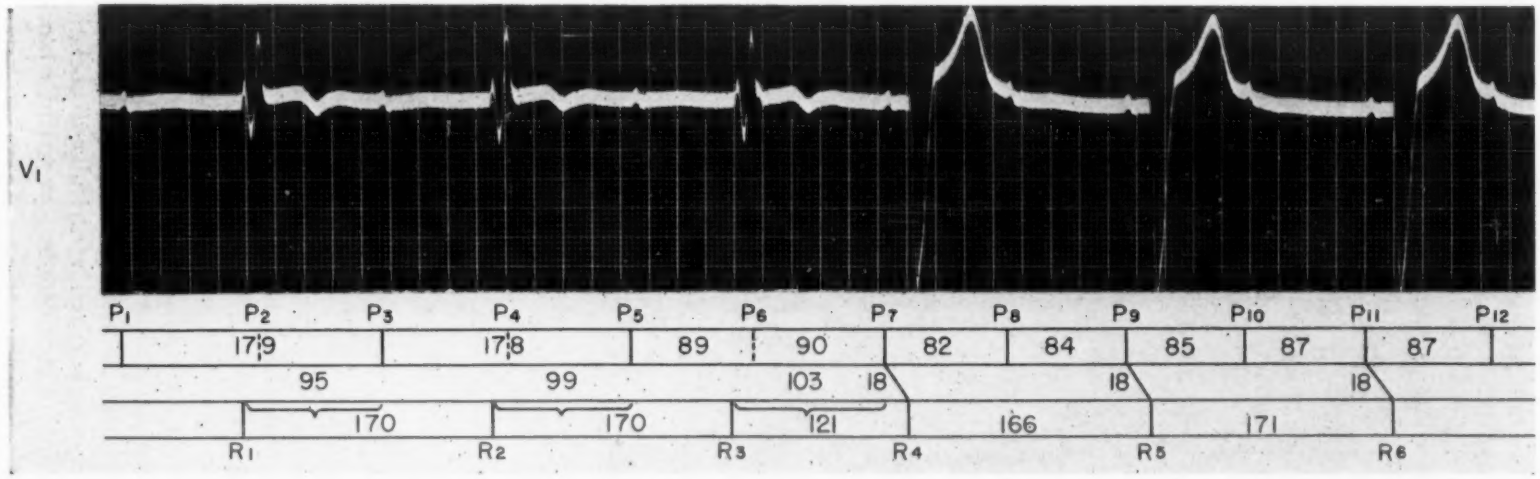
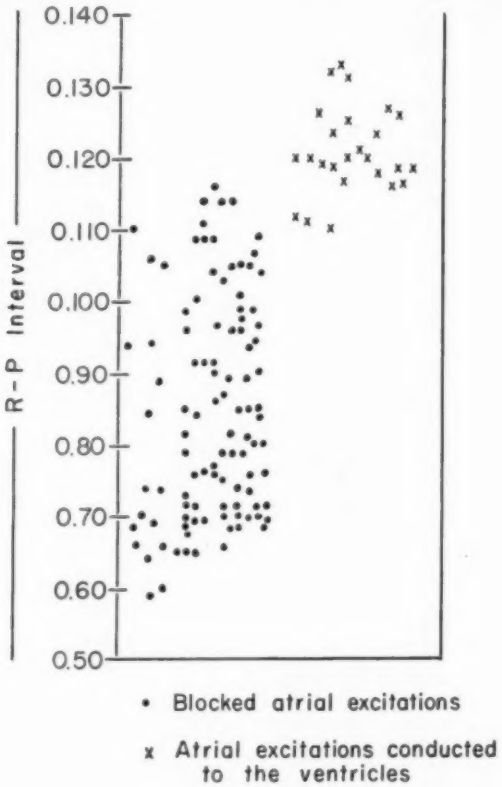


Fig. 6 (Case 2).—Lead V_1. The tracing shows transition from atrioventricular dissociation to undisturbed 2:1 atrioventricular block. P_3 and P_5, which fall 0.95 and 0.99 seconds, respectively, after the automatic ventricular beat, are blocked. P_7 has an R-P interval of 1.03 seconds and is conducted to the ventricle. The transmitted atrial excitation discharges prematurely and inhibits the automatic ventricular center. Therefore, two more atrial impulses, P_9 and P_{11}, have a chance to be conducted to the ventricles (atrioventricular block 2:1). The conducted beats show features consistent with left bundle branch block; the independent beats present signs of delayed activation of the right ventricle.

In the presence of dissociation with interference, the ventricular cycle after the conducted beat may have the same length as the average automatic ventricular period (Case 1). Sometimes it is longer (Case 2) when, namely, the atrial excitation by prematurely discharging the ventricular center exerts an inhibiting effect on the latter. Even shortening of the ventricular cycle after conduction of a sinoauricular impulse has been observed. This happens when the sinus excitation, after discharging the ventricular pacemaker, suffers a delay of conduction in the junctional tissues because of its prematurity, while the following automatic ventricular impulse finds the conductive tissues rested after a longer pause and has a shorter transmission time.[7]

TABLE I. COMPARISON OF THE R-P INTERVALS OF 102 BLOCKED AND 25 CONDUCTED SINOAURICULAR EXCITATIONS WHICH FOLLOW AUTOMATIC VENTRICULAR BEATS



Theoretically, dissociation with interference may occur also in the presence of 3:1 block, or even with higher degrees of atrioventricular block. However, when the refractory period of the bundle is very long, it is likely that complete atrioventricular dissociation will develop rather than dissociation with interference[3] for reasons which have been indicated above. Complete atrioventricular dissociation of such origin is probably more common than is realized. It has been repeatedly stressed[3-5,8] that an attempt should be made to distinguish complete atrioventricular block from complete atrioventricular dissociation. The latter may be present in the absence of complete atrioventricular block, or even of a partial atrioventricular block, for that matter.

The clinical significance of dissociation with interference in the presence of atrioventricular block is not different from that of uncomplicated atrioventricular block.

SUMMARY

Two cases are reported which present dissociation with interference in the presence of 2:1 atrioventricular block. This arrhythmia differs from ordinary dissociation with interference in that the automatic ventricular rhythm is slower than the sinus rhythm, but is faster than the sinoauricular half rhythm.

Dissociation with interference combined with 2:1 atrioventricular block is a well-defined arrhythmia which shows the following characteristic features:

1. Dissociated action of the atria and ventricles. The regular ventricular rhythm is occasionally interrupted by shorter ventricular cycles.
2. The ventricular complexes which conclude the shorter cycles show a fixed relationship to a preceding atrial wave, thus suggesting that they are due to conducted atrial excitations. They may or may not differ in shape from the regular ventricular beats.
3. The P wave of the conducted beats show a distinct time relationship to the preceding automatic ventricular beat. Only those atrial impulses are conducted which fall late in diastole after the refractory state of the bundle, caused by transmission of an automatic ventricular excitation, has ended.
4. The refractory period of the bundle can be estimated from the shortest R-P interval of the conducted sinoauricular beats. This "critical" R-P interval may be close to, but is mostly longer than, one sinus period.

Complete atrioventricular dissociation develops instead of dissociation with interference when the critical R-P interval plus the time required for conduction of a sinoauricular excitation is longer than the automatic ventricular period. Complete atrioventricular dissociation of this type should not be mistaken for complete atrioventricular block.

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THE DUAL DISPLACEMENT AND VELOCITY BALLISTOCARDIOGRAPH APPARATUS

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THE SIMPLE, portable, and inexpensive direct body type apparatus, recently devised by Dock and Taubman,[1] has apparently converted ballistocardiography into a practical, routine clinical procedure in cardiac diagnosis. The instruments previously used, such as the tables of Starr and associates,[2] Nickerson and Curtis,[3] and Brown and Pearson[4] were bulky, costly, and complicated, and required fixed installation. Ballistocardiography, therefore, was hitherto limited to only a few research centers.

The value of ballistocardiography in clinical medicine has been established empirically on the qualitative appearance of the component waves of the ballistocardiographic tracings by both the older[2,5-11] as well as by the new direct method.[12-18] Quantitative studies, to evaluate cardiac output by means of ballistocardiography, have been reported in the past.[2,19-22] However, quantitative output determinations with the new direct ballistocardiographic technique have heretofore not been attempted nor deemed advisable.[21] A weighted pendulum had been proposed for rough standardization by Dock and Taubman.[1] The weight is dropped against the shoulder from a fixed point while the ballistocardiographic record is being taken and the resultant lowering of the base line is related to the force applied. However, precise standardization of the apparatus is not available.

The Dock method of direct body type ballistocardiography records longitudinal body oscillations, incident to the contraction of the heart and the expulsion of the blood with each cardiac cycle. With the patient supine on an immobile table, the resultant body movements are transmitted through a crossbar on the shins to a hinge which regulates the amount of light falling on a barrier layer photoelectric cell device. By connecting the latter to the "right arm" and "left arm" cable terminals of an electrocardiographic machine, one may record the displacement (photoelectric) ballistocardiogram with the selector switch on standard Lead I. Velocity (electromagnetic) ballistocardiograms may be recorded by placing a crossbar on the shins in contact with a hinge containing a coil of wire. The coil moves in a magnetic field produced by a stationary Alnico magnet. Connection of the coil to the standard Lead I wires of the electro-

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cardiographic machine cable serves for recording the velocity tracing. A third, piezoelectric method, utilizes a metal bar on the shins in contact with a hinge which actuates glennite crystals, thereby producing the ballistocardiographic tracing.[24] Objections to the latter include the relatively heavy weight of the crossbar needed as well as the fact that the resultant ballistocardiographic tracings may not be uniform since the records will depend upon the angle of contact of the crossbar with the hinge. Hinge arrangements are at best poor, and we have eliminated them in the dual ballistocardiograph (see below).

Simultaneous cardiac events may be recorded with the ballistocardiogram for accurate identification of the individual waves. This is necessary only with bizarre ballistic tracings. Since the QRS of the electrocardiogram precedes the ballistocardiographic waves, the electrocardiogram may be taken superimposed on the ballistocardiographic tracing by connecting the electrocardiogram (Lead I) in series with the terminals from the ballistocardiographic pickup.[15] This serves for timing purposes, even with the commonly employed single-channel electrocardiographic machines.

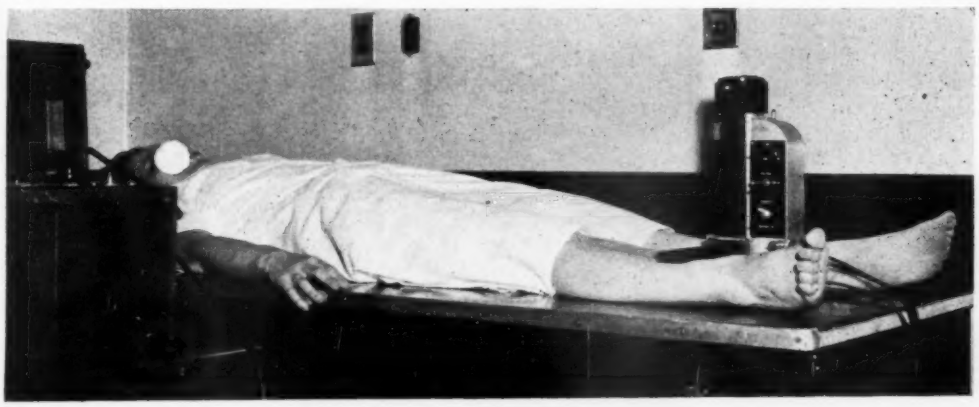

Fig. 1.—Technique for recording direct body ballistocardiograms modified after Dock. The patient lies supine on an immobile table and the tracing is recorded from a crossbar on the shins.

If the displacement and the velocity recording devices were free from any inherent distortions, the latter curve would be a first derivative of the former (the amplitudes of the deflections on the velocity tracings represent the slopes of the curves of the displacement tracings). Due to the complexity of the ballistocardiographic tracings, the main apparent difference between the displacement and velocity curves is a phase shift with the displacement curve lagging behind the velocity curve. The magnetic device used for velocity tracings is extremely sensitive to body tremor; in order to dampen these out, we use a 20 microfarad condenser parallel to the pickup. This introduces alterations in the magnetic pattern, including phase shift, thus making it appear that both displacement and velocity graphs are in phase. This artifact must be kept in mind when analyzing the time relationships of these graphs.

Investigation was undertaken to study the difference in appearance of ballistocardiographic tracings taken by the photoelectric and the modified electromagnetic apparatus (with the 20 microfarad condenser). One of us (L.P.)

devised a standardized dual ballistocardiographic apparatus* for this purpose (Figs. 1 and 2). The hinges, as described by Dock and Taubman,[1] were eliminated completely, and the Alnico magnet was placed within the crossbar. Thus, the crossbar lies on the patient's shins with the remaining portions free in space. The edge of the crossbar partially occludes the light on the photocell. The wire coils with iron cores are placed in front of the Alnico magnet below and behind the light source. Thus, ballistocardiographic records of the displacement and velocity types may be recorded either simultaneously or successively, without a hinge, and with a single placement of the crossbar.

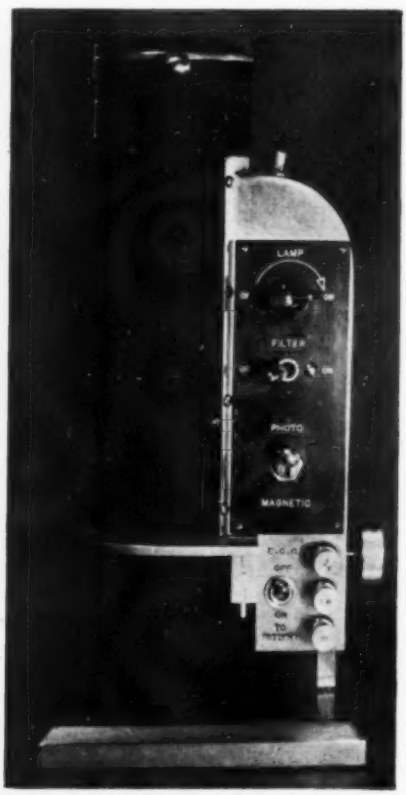

Fig. 2.—The dual ballistocardiograph apparatus. Side view.

Simultaneous ballistocardiographs, taken in this manner, show marked qualitative differences between the photoelectric and the electromagnetic records. The equality of the J-K swing has no interpretative value, since the amplitude of the velocity tracing is controlled by magnet-coil distance which is adjusted to give amplitudes comparable to the displacement record.

*Manufactured by the Mendelsohn Speedgun Company, Bloomfield, N. J.

In the photoelectric displacement record of normal subjects (Fig. 3), the amplitude of the I wave is usually slightly less than that of the K wave. In simultaneously taken electromagnetic tracings, the I wave may be one-third to one-half as deep as the K wave (Fig. 3). In cardiac patients, the differences in the two types of records may be more marked (Figs. 4 to 6).

Interpretation of ballistocardiograms on the basis of qualitative appearance rests purely on empirical correlation with the clinical picture. It is deemed advisable, therefore, to record both the displacement and velocity tracings in all cases studied. The criterion for abnormal I waves with the photoelectric (displacement) technique (I wave less than 15 per cent of the amplitude of the main J or K deflection) differs from that for the velocity (electromagnetic) tracings (I wave extremely small or absent). This was determined by comparison of the two types of tracings in well over 200 normal records.

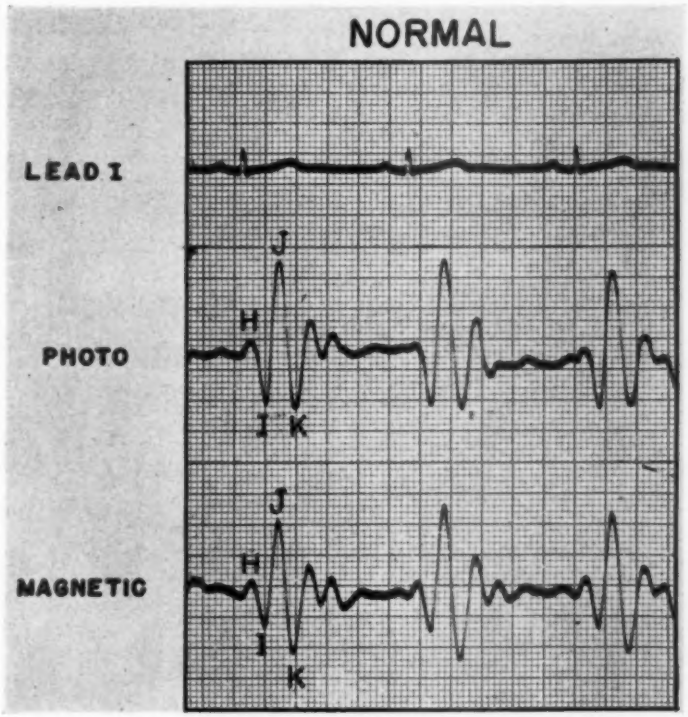

Fig. 3.—E. D., a 33-year-old normal man. Synchronous record of photoelectric (displacement) and electromagnetic (velocity) ballistocardiograms with Lead I. Note differences in I waves with the two methods.

The establishment of standardized recording conditions with this apparatus was deemed important and this was achieved by connecting a microammeter with the photocell terminals. The rheostat knob controlling the light intensity is turned on and rotated in a clockwise direction until the reading is 100 microamperes. The crossbar is then placed between the light source and photocell

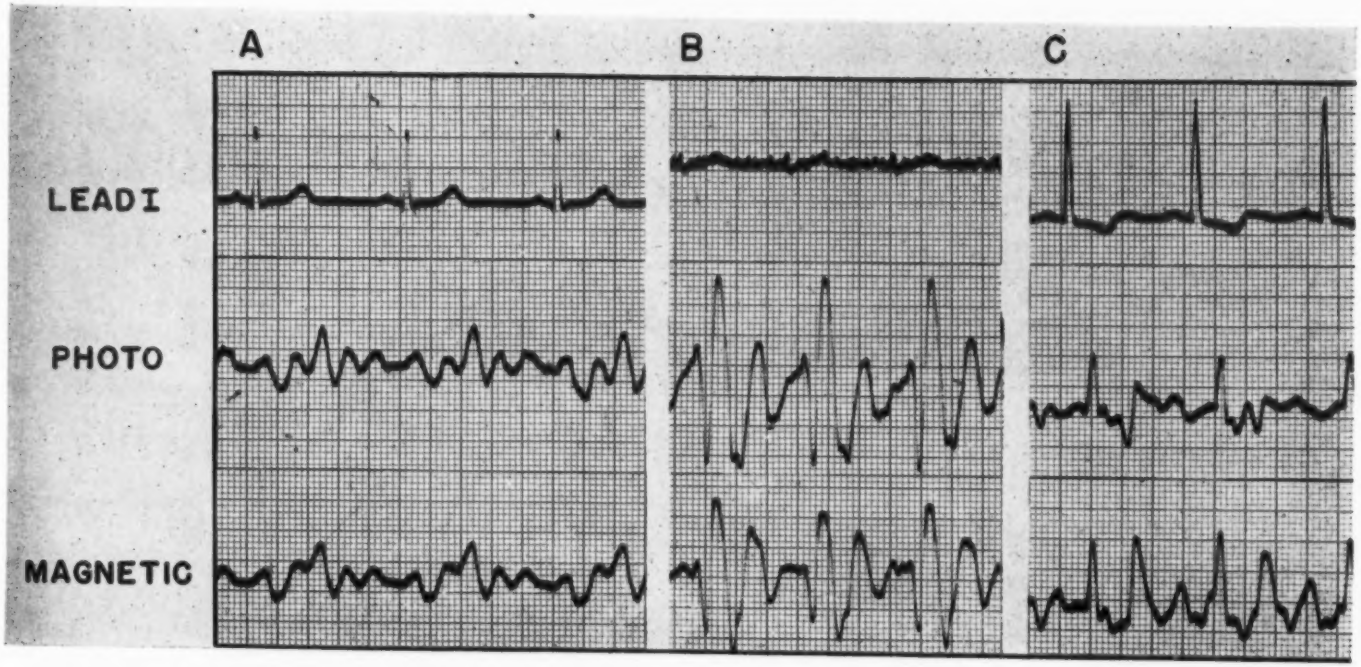

Fig. 4.—Synchronous records of photoelectric (displacement) and electromagnetic (velocity) ballistocardiograms with Lead I. *A* and *B*, Patients with angina pectoris. *C*, Patient with hypertensive heart disease. Note qualitative differences with the two methods.

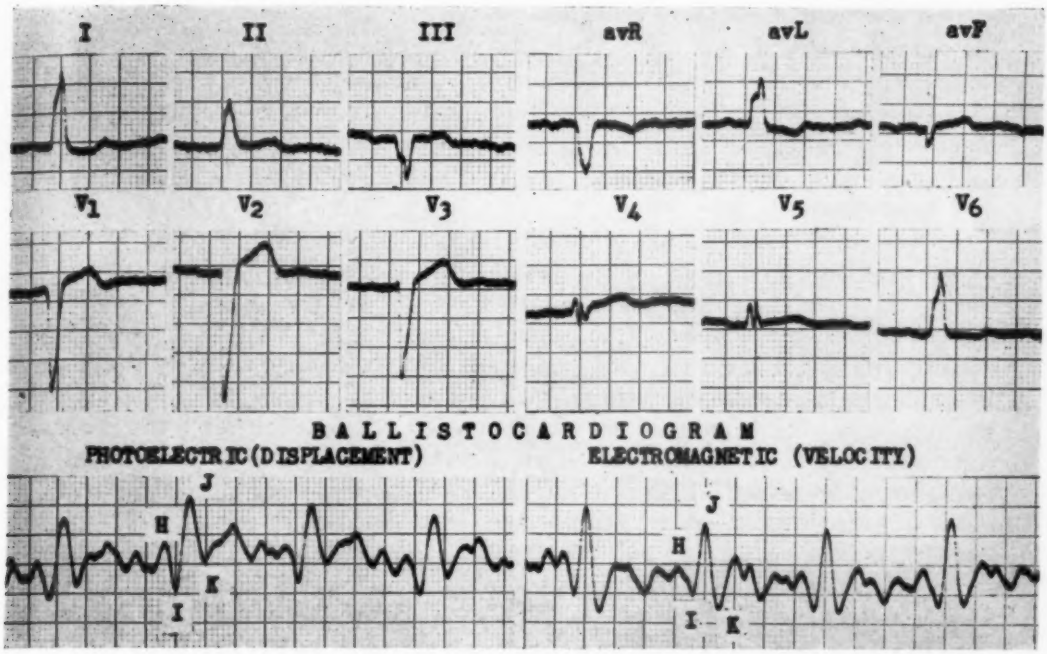

Fig. 5.—L. H., a 56-year-old woman. Arteriosclerotic heart disease, left ventricular enlargement. Electrocardiogram showed left bundle branch block. Photoelectric (displacement) ballistocardiogram; abnormal—short K wave; but electromagnetic (velocity) ballistocardiogram: normal.

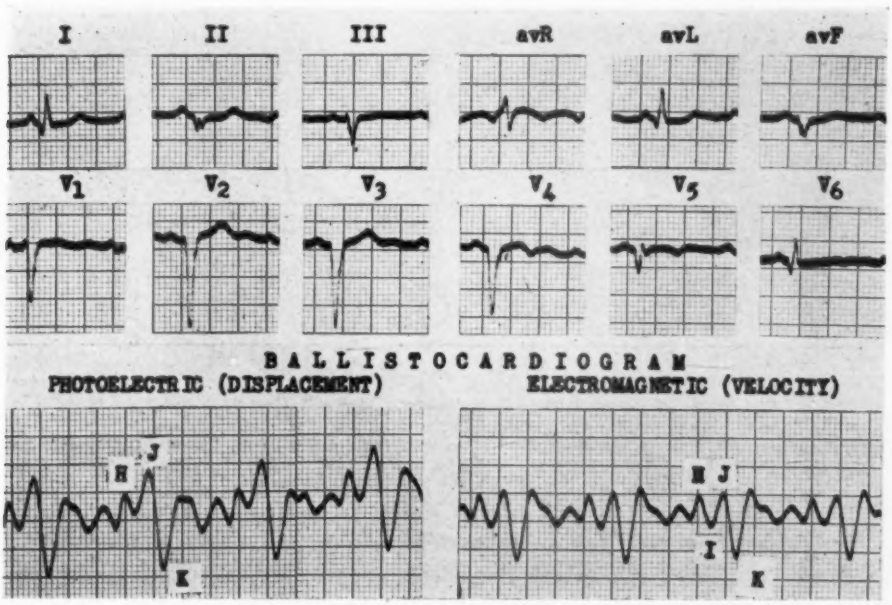

Fig. 6.—P. K., a 40-year-old man. Arteriosclerotic heart disease; angina pectoris. Electrocardiogram showed previous myocardial infarction, anterior and posterior (6 months); Q waves, and T alterations. Photoelectric (displacement) ballistocardiogram: abnormal—small I wave; but electromagnetic (velocity) ballistocardiogram shows early "M" pattern.

so that the light is partially occluded. When the reading is 10 microamperes, the machine is ready for use. All ballistocardiographic records taken by this simple technique can thus be standardized and made consistently reproducible.

A precise standardization of the ballistocardiographic setup requires a dynamic calibration of the photocell and magnetic devices by a controlled mechanical movement of our crossbar with a linear reciprocating linkage. This work is now in progress.

The photoelectric tracings (unfiltered) may have the advantage of producing a linear response to movements of the crossbar. Respiration, however, must be suspended while the record is made with the photocell technique. In practice, therefore, these records should be taken following slight inspiration, then after deep inspiration, and finally deep expiration. A condenser-resistor system may be employed as a respiratory filter with photoelectric recordings. The use of the respiratory filter reduces the low frequency response, thereby eliminating respiratory effects on the base line. Unfortunately, this introduces an appreciable alteration in the record and should be reserved for cases with respiratory difficulty.

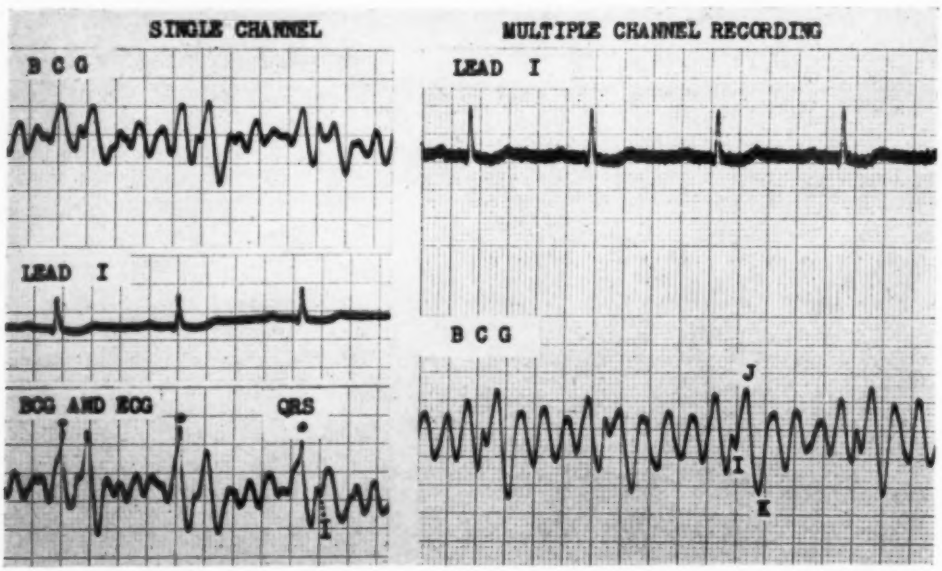

Fig. 7.—I. S., a 73-year-old man. Arteriosclerotic and hypertensive heart disease. Electrocardiogram showed left ventricular "strain" pattern. Ballistocardiogram showed component waves not readily identifiable on single-channel recording. Abnormal small I wave noted 0.12 to 0.14 second after QRS complex in both single- and multiple-channel record of simultaneous ballistocardiogram and electrocardiogram, illustrating the necessity for proper time reference of ballistocardiogram tracings.

Electromagnetic records do not display a linear response to motion of the crossbar, but respiration need not be suspended while the tracing is recorded. A 20 microfarad condenser is used for the electromagnetic records (to dampen body tremor); the condenser may be removed for true velocity recordings.

The recording technique with the dual apparatus is simple and standardized. Highly critical adjustment for the photocell pickup is no longer a tenable objec-

tion to its use. Previously described electromagnetic devices[12] required close apposition of magnet to wire coil. Beyond the distance of 2 to 3 mm., suitable tracings heretofore could not be recorded. Working within this highly critical distance, one could obviously not obtain standard electromagnetic tracings. Due to the use of two coils and of iron cores in the coils the voltage output in the ballistocardiographic apparatus described is increased manifold and excellent electromagnetic records can be taken, with a working distance greater than one-half inch.

Simultaneous electrocardiographic tracings may be inserted with this apparatus, for timing reference, in any individual case with a bizarre record (Fig. 7).

The dual apparatus described is easily adaptable for taking lateral, anteroposterior, and vector ballistocardiographic tracings.

SUMMARY

1. A dual ballistocardiograph apparatus for recording simultaneous or successive displacement (photoelectric) and velocity (electromagnetic) ballistocardiograms is described.

2. The technique for establishing reproducible standardized conditions for ballistocardiographic tracings is described; work is in progress on standardization of recording equipment.

3. A respiratory filter (for photoelectric tracings) as well as simultaneous electrocardiograms may be utilized by a simple switch arrangement.

4. Lateral and anteroposterior ballistocardiographic tracings, as well as the customary longitudinal ones, may be recorded with the new apparatus.

CONCLUSION

The dual displacement and velocity ballistocardiograph apparatus is presented as a practical, portable, and standard instrument for recording Dock type direct ballistocardiograms routinely.

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BALLISTOCARDIOGRAPHIC RESPONSE TO NITROGLYCERIN IN CORONARY ARTERY DISEASE

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IN HIS cadaver experiments, Starr[1] demonstrated, by simultaneous injection into the aorta and the pulmonary artery, that the normal IJK complex of the ballistocardiogram occurs when the maximum velocity of blood ejection is attained early in systole. The scarred myocardium, unable to exert the necessary force, causes the velocity of ejection to be built up slowly, the peak velocity occurring late in systole. The earliest loss of myocardial vigor is demonstrated by changes in the ballistocardiogram: specifically, diminution or notching of the J wave, shortening of the I-J stroke, with increase in the prominence of the K wave. Extremes of myocardial weakness result in ballistocardiographic waves of low amplitude and indefinable pattern. All of these ballistocardiographic abnormalities may occur in subjects with coronary artery disease without necessarily indicating a decrease in the cardiac output.[1]

One of the most useful attributes of ballistocardiography results from the fact that the great majority of subjects with symptomatic coronary artery disease will have sufficient myocardial inefficiency to demonstrate these abnormal ballistocardiographic patterns either at rest or after exercise.[2-4] Our purpose, in this report, is to describe the ballistocardiographic changes we have noted in subjects with coronary artery disease and abnormal resting ballistocardiograms after the use of nitroglycerin to relieve angina pectoris induced by mild exertion. The drug, coincident to providing relief from the anginal pain, caused a reversion in the ballistocardiogram toward a normal configuration in several instances.

The effect of nitroglycerin upon the ballistocardiogram in normal subjects was found by Wegria and associates[5] to be a marked increase in the amplitude of the IJK complex. This was apparently a contradiction of previous experimental results,[6] which showed that nitroglycerin produced no change in the minute volume output of the heart and caused a slight decrease in the stroke volume output. The discrepancy was explained by Brandt and associates[7] by simultaneous kymographic and ballistocardiographic studies which indicated that diminution of ventricular excursion and volume accompanied the increased ballistocardiographic complexes produced by nitroglycerin. They inferred that the striking increase in the IJK complex must result from the decrease in peripheral resistance brought about by the drug, enabling a greater initial ejection velocity to be achieved by the normal myocardium.

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In our study of patients with coronary artery disease, the exercise test provoked attacks of angina pectoris in several instances. Relief was obtained by nitroglycerin placed under the tongue. A ballistocardiogram was obtained immediately upon subsidence of the attack. We were then able to compare the resting basal ballistocardiogram with that obtained when relief from angina was obtained by the use of nitroglycerin.

Striking improvement was noted in the ballistocardiogram, as shown by a lengthening of the H-I stroke, increase in the amplitude of the complexes, and the appearance of a sharply peaked J in contrast to the notched J. These effects, following the use of nitroglycerin, may be due to increased coronary artery blood flow[8] with relief of anoxia and greater myocardial efficiency. A minority of the patients with angina, so tested, showed no changes in the ballistocardiogram.

ILLUSTRATIVE CASES

The portable electromagnetic ballistocardiograph[9] was the recording instrument in these studies. The upper trace is the ballistocardiogram; the lower channel represents the radial pulse trace. The J waves occur at the apex of the pulse trace.

CASE 1.—A.L., 56 years of age, has had hypertension and angina pectoris for six years. Repeated studies, electrocardiograms, teleroentgenogram, and intravenous pyelograms were all normal. He suffered an anterior wall myocardial infarction in August, 1951. There were two months of complete bed rest. Since then, any slight effort induces angina. On Nov. 3, 1951, blood pressure was 170/100 mm. Hg. The heart was slightly enlarged; there was gallop rhythm. The electrocardiogram showed the residual of an anterior myocardial infarction.

Ballistocardiogram (Fig. 1): *A*, Basal: short HIJ, deep K pattern, with prominent L waves characteristic of gallop.

B, Patient attempted the exercise test; after four trips, he complained of severe angina. Nitroglycerin, 1/100 grain, was placed under the tongue. One minute later, tracing *B* was recorded. The pulse rate was unchanged. The blood pressure was 165/95 mm. Hg. (Note improved amplitude of expiratory complexes; each complex is definitive.)

CASE 2.—P.B., 58 years of age, has had known hypertension for several years. He suffered an anterior wall myocardial infarction in 1947, and again in 1949, with disabling angina on effort since. Relief was obtained by 1/50 grain of nitroglycerin. On Nov. 1, 1951, the weight was 132 pounds, blood pressure 160/90 mm. Hg, and the heart was not enlarged. The electrocardiogram showed the residual of an anterior myocardial infarction.

Ballistocardiogram (Fig. 2): *A*, Basal: Brown Grade III; notched J waves, or coved J waves; all complexes of low amplitude.

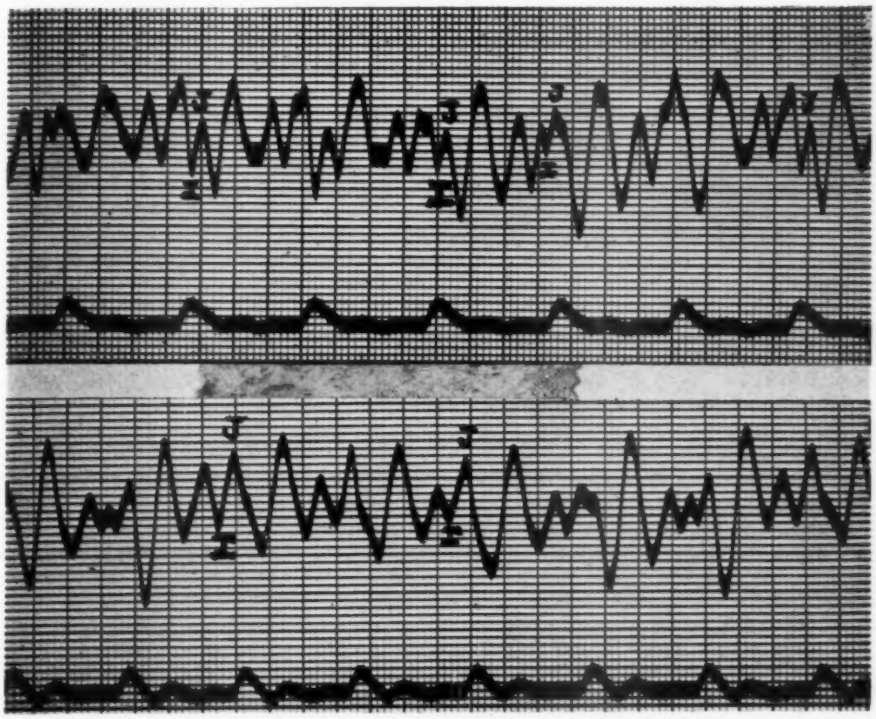
Exercise test was started; after four trips, patient developed angina pectoris; two 1/100 grain nitroglycerin tablets were placed under the tongue and relief occurred after two minutes; then *B* was recorded.

B, The pulse rate increased; the blood pressure was 165/90 mm. Hg; HI and IJ had good amplitude, J becoming prominent; notched J waves were no longer present; L waves were reduced in amplitude.

SUMMARY

In studies on subjects with coronary artery disease, the exercise test caused angina pectoris in several instances. Nitroglycerin provided relief.

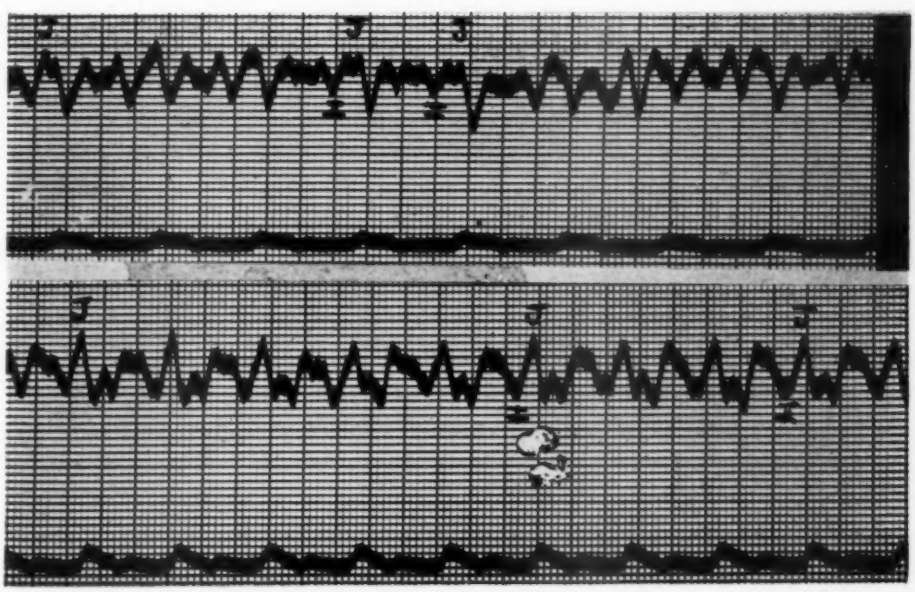
Ballistocardiograms were recorded at the moment angina had subsided and compared with traces taken under basal conditions. Striking improvement in the



A.

B.

Fig. 1.



A.

B.

Fig. 2.

ballistocardiogram was noted after nitroglycerin in the majority of cases; occasional subjects demonstrated no ballistocardiographic improvement after using the drug.

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THE FUSION FREQUENCY OF FLICKER IN HYPERTENSION

A Study of Its Application to the Estimation of Hypertensive Cardiovascular Disease

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THE FUSION frequency of flicker is defined as the frequency of flickering light at which a subject perceives it as continuous illumination. This frequency is believed to be an index of function of the retinocortical system. Fusion frequency of flicker is influenced by age, physical and mental fatigue or anxiety, administration of drugs, brain lesions, hypothyroidism, and circulatory insufficiency.

Enzer, Simonson, and Blankstein[1] determined the fusion rates of forty-seven normal subjects and of twenty-two patients "with circulatory insufficiency." The rate for the control group was 44.9 per second and that for the test group was 36.1. Nine of the twenty-two patients had hypertension; of these three had visual impairment. There was no relation between blood pressure and decrease in fusion frequency in hypertensive patients with normal vision. Of the three patients with decreased visual acuity, two had greatly depressed fusion rates. Of these two, one had advanced retinal arteriosclerosis. Three nonhypertensive patients with retinal arteriosclerosis were studied and two of these had markedly depressed fusion rates. Thus, local retinal vascular disease accounted for some of the low values observed. Since proper function of the optic pathways and cortex depends upon adequate oxygen supply the decrease in fusion rate in the absence of retinal disease was attributed to cerebral anoxia from local or systemic circulatory insufficiency. In support of this they cited a case of pernicious anemia in relapse whose fusion frequency was depressed.

Other than measurements of cerebral blood flow[2] there are no objective measures of hypertensive cerebrovascular disease. The present study was made to determine if fusion frequency of flicker could serve as a means of detecting incipient cerebral vascular insufficiency. The assumption was that cerebrovascular disease might consistently depress the retinocerebral functions involved in flicker fusion. Second, since anoxia is known to depress fusion rate, a comparison was made in normal and hypertensive subjects of the effects of anoxia on fusion frequency of flicker. The hypothesis here was that the depressant effect of anoxia would be intensified in the presence of cerebral arteriosclerosis or

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vasospasm so that graded anoxia should result in a precipitate fall of fusion frequency of flicker in hypertensive vascular disease but not in normal subjects.

As this study was completed, the change in fusion frequency of flicker which follows on administration of nitroglycerin was recommended as a means of detecting subclinical arteriosclerotic heart disease[3] and, more recently, in the examination of patients with "vascular hypertonus," such as results from exposure to cold.[4] The concept underlying these proposals is that these forms of cardiovascular dysfunction are associated with retinal vasospasm severe enough to cause marginal anoxia of the retina; nitroglycerin is presumed to relieve the vasospasm and anoxia and thereby increase fusion frequency of flicker. Surveys in patients with hypertensive and arteriosclerotic heart disease have not confirmed the association of "abnormal" fusion frequency of flicker response with cardiovascular disease.[5,6,7] The effect of anoxia as such has not been critically examined, although its presence and relief by nitroglycerin is the presumed mechanism of an "abnormal" response. The present study deals primarily with the effects of anoxia on fusion frequency of flicker in patients with severe essential hypertension.

METHOD AND MATERIAL

The method employed in determining fusion frequency, while similar in principle to that of other investigators, was modified to increase accuracy.[8] Increment of flicker rate was mechanically controlled by a constant speed motor, and the fusion point was indicated by the subject's closing of a key, this action simultaneously freezing and recording flicker rate. Thus, subjective responses, conscious or unconscious on the part of the observer, were completely eliminated from the procedure.

As a control, the fusion rate was determined in fifty healthy adults whose ages ranged from 15 to 70 and averaged 30.5 years. None of these had arterial hypertension. The test group consisted of twenty-nine patients admitted to the hospital for hypertension. Their ages ranged from 21 to 60 with a mean of 45.2 years. Their fundi were examined and graded at the time of the test. A third group of twenty-six normotensive hospitalized patients were also tested. These patients served as a control group living under the same environment but suffering from an illness other than hypertension. Their ages ranged from 21 to 70 and averaged 51.9 years.

After the determinations of fusion frequency of flicker, arterial oxygen content was varied by having the subject breathe through a BLB mask variable mixtures of oxygen and nitrogen. Four controlled readings were carried out while the patient was breathing room air. The mask was then applied and 100 per cent oxygen administered. The fusion rate was again determined four times. A Coleman anoxia-photometer* was then fastened to an ear helix and set at 100 per cent saturation. The nitrogen fraction in the gas mixture was then increased. At least three determinations of the fusion frequency were made at 90, 85, and 80 per cent arterial oxygen saturation as indicated by the anoxia-

*Generously supplied to the Research Division, Cleveland Clinic Foundation, for investigational purposes by Mr. E. D. Coleman, Coleman Instrument, Inc., Maywood, Ill.

photometer. The oxygen deprivation was then increased either to a 75 per cent arterial oxygen saturation or to a point where dizziness occurred, and tachycardia, tachypnea, and cyanosis were observed. Individual variations in the response to anoxia were seen. One normal subject became nauseated, confused, cyanotic, developed a slight clonic tremor of the hands and perspiration at 75 to 80 per cent arterial oxygen. Oxygen (100 per cent) was administered immediately. Consciousness and feeling of well-being returned in thirty seconds.

RESULTS

1. *Comparison of Normotensive and Hypertensive Persons Breathing Room Air.*—As noted in Table I, the mean flicker fusion frequency for the fifty normal individuals was 34.3 cycles per second (C.P.S.). That of the hypertensive group was 32.0 C.P.S. The standard error of the difference between the two means is 0.70; the difference between the means of 2.3 C.P.S. could have occurred by chance only once in approximately 400 times.

TABLE I. AGE DISTRIBUTION AND CORRESPONDING MEAN FUSION FREQUENCY OF FLICKER

GROUP		DECADE						TOTAL
		2 (15-19 YRS.)	3 (20-29 YRS.)	4 (30-39 YRS.)	5 (40-49 YRS.)	6 (50-59 YRS.)	7 (60-69 YRS.)	
Normal Control	No. of Patients	2	31	9	4	3	1	50
	Mean FFF	33.3	34.6	33.8	33.8	32.0	36.9	34.3
Hypertensive	No. of Patients	0	1	6	11	10	1	29
	Mean FFF		31.4	32.8	31.6	31.7	35.0	32.0

Fusion frequency of flicker (FFF) is stated in cycles per second (C.P.S.).

The mean age for the individuals in the control group was 30.5 years and the mean age in the hypertensive group was 45.2 years, so that the difference in the flicker fusion rate might be attributed to the difference in age. Some[9,10] have found that the fusion rate decreases with aging only in the late forties. Simonson and associates,[11] however, found a difference between the third and fourth decades which we did not. As seen in Table I, there is a difference between the normal and hypertensive patients of 1 C.P.S. in the fourth decade, 2.2 C.P.S. in the fifth, and 0.3 in the sixth. It is unlikely that age alone is responsible for the consistently lower fusion frequency of flicker in the hypertensive group in view of the decrease in the mean value in the normal group for corresponding decades. Consequently, the depression of the fusion frequency of flicker in the hypertensive group is attributable to cerebrovascular disease and, in so far as aging is a factor, may represent the advanced physiologic age of the cerebral blood vessels in hypertensive patients.

The mean fusion frequency of flicker of 34.8 C.P.S. for the normotensive hospitalized patients differs from the mean fusion frequency of flicker of 37.28 for the control readings of the normal group studied under anoxia by 2.48 C.P.S. These and subsequent subjects were done under slightly different experimental conditions from the preceding groups and, as a result, the normal mean was taken as 37.28 C.P.S. rather than 34.3. The difference of 2.48 cycles between normal control subjects and hospitalized normotensive patients is not significant (Table II). Therefore, the hospitalization of the hypertensive group of patients and a regime of adequate bed rest, diet, sedation, etc. is probably not responsible for the decrease in the fusion frequency of flicker which they manifest.

TABLE II. STATISTICAL SUMMARY OF FUSION FREQUENCY OF FLICKER IN NORMAL AND HYPERTENSIVE SUBJECTS

GROUP	NUMBER OF PATIENTS	MEAN	STANDARD DEVIATION	STANDARD ERROR OF THE MEAN	DIFFERENCE BETWEEN TWO MEANS	STANDARD ERROR OF DIFFERENCE BETWEEN TWO MEANS	Δ
			σ	σ_m	Δ	S.E. Δ	S.E. Δ
Normal	50	34.31	2.45	3.346	2.28	0.70	3.2
Hypertensive	29	32.03	3.34	0.620			
Normotensive Hospitalized	26	34.80	6.33	1.24	2.48	2.05	1.20
Normal Anoxia (Control)	9	37.28	4.93	1.64	0.10	2.16	0.04
80% Arterial Oxygen Saturation	9	37.18	4.24	1.41			
Hypertensive Anoxia	10	35.05	4.13	1.30	0.99	1.69	0.58
80% Arterial Oxygen Saturation	10	34.06	3.20	1.01			

The formulas used are described by Hill.[12] The standard deviations were calculated using the formula for small groups.

There was no correlation between the fundus findings and the fusion frequency in the hypertensive group. The fusion frequency of patients with Grade IV (Keith-Wagener) eye grounds ranged from 29 to 38.5. Patients with Grade II eye grounds had rates from 26 to 35. All patients with moderate to severe retinal damage stated they could easily see the flickering light at a low frequency. This was borne out by the reproducibility of their fusion rates.

One 56-year-old patient, with Grade III eye grounds, was admitted following a cerebral hemorrhage with grossly bloody spinal fluid. During convalescence his flicker fusion rate was 31.4. An attempt was made to increase cerebral blood flow with bilateral stellate blocks. His fusion rate ten minutes after the physiologically successful blocks was 29.9. Another 56-year-old patient, who was being treated for Parkinsonism associated with arteriosclerosis also received

successful bilateral stellate blocks. His fusion rate before was 30 C.P.S. and ten minutes after was 28.7 C.P.S.

2. *Effects of Anoxia.*—Of the nine normal individuals in the control anoxia group, the differences in flicker fusion rate at 90 and 85 per cent arterial oxygen were slight. Administration of 100 per cent oxygen had no effect. All subjects were brought to an oxygen saturation of 80 per cent. Control fusion rates while the patients were breathing room air were compared with the rates at arterial oxygen saturation of 80 per cent. The mean fusion frequency for the control group was 37.28 C.P.S. At 80 per cent arterial oxygen, the mean fusion frequency was 37.18 C.P.S. This difference is insignificant (Table II). Three of the four individuals in the group subjected to still lower arterial oxygen levels sustained a fall in the fusion frequency (Table III). All of these experienced symptoms of anoxemia at the lowest level.

TABLE III. FUSION FREQUENCY OF SUBJECTS IN CONTROL AND TEST GROUPS SUBMITTED TO ARTERIAL OXYGEN SATURATIONS LESS THAN 80 PER CENT

GROUP	PATIENT	FUSION FREQUENCY OF FLICKER AT:				
		CONTROL	80% ART. OXYGEN SAT.	75% ART. OXYGEN SAT.	70% ART. OXYGEN SAT.	65% ART. OXYGEN SAT.
Control anoxia	R. J.	33.5	33.4	32.3		
	A. D.	40.9	41.6	40.6		38.0
	G. M.	32.9	33.8	32.3	31.6	
	C. S.	39.9	38.7	37.0		
Hypertensive anoxia	J. A.	34.2	33.3	32.6		
	C. F.	30.6	31.3	29.9		
	F. H.	33.6	32.7	32.5		
	L. K.	35.6	33.7	34.0		
	T. P.	31.8	32.7	33.0		
	C. S.	39.6	37.4	35.5		

Fusion frequency of flicker is stated in cycles per second.

There were ten hypertensive patients subjected to anoxia. The control mean fusion frequency of flicker was 35.05 C.P.S. and the mean fusion frequency of flicker at 80 per cent arterial oxygen saturation was 34.06 C.P.S. The difference between these means (0.99 C.P.S.) is not significant. One 60-year-old patient, who had Grade IV eye grounds, complained of precordial pain at an oxygen saturation of 90 per cent. He was given 100 per cent oxygen and the pain was relieved within three minutes. Six patients in this group were subjected to arterial oxygen levels below 80 per cent. The fusion rates are listed ni Table III. One 40-year-old patient, with malignant hypertension and Grade IV eye grounds, had a higher fusion rate at 75 per cent than when breathing room air. This was the only subject to show such a paradoxical response.

DISCUSSION

A difference has been demonstrated between the mean fusion frequency of flicker of normal and hypertensive persons breathing room air.

As to the cause of this difference, it has been shown[13] that the visual system is one of the first to be affected by anoxia. If there were a subcritical cerebral anoxia in hypertensive patients as a result of arteriosclerosis or vasoconstriction, they should manifest a precipitate drop in visual function when arterial oxygen saturation is abruptly decreased. Actually, the hypertensive patient's reaction to anoxia is no different from that of the normal subject. Since this is the case, the depressed fusion frequency of flicker in hypertension more probably represents focal tissue deterioration than diffuse subclinical cerebral or retinal ischemia and anoxia. A corollary is the probability that the decrease in the fusion frequency of flicker found in older people is not due to age-conditioned functional anoxia but is a manifestation of local organic deterioration of the retinocortical system.

The cervical sympathetic blocks were given with the intention of altering the cerebral circulation. A definite Horner's sign was elicited in each case. Contrary to what was expected, the fusion frequency of flicker fell in both instances of stellate block. We have been unable by retinal photography in two patients to demonstrate changes in retino-arteriolar spasm after unilateral stellate block. Thus, this procedure does not seem to release such vasospasm as may occur in the retinocerebral system. Moreover, stellate blocks produce no increase in total cerebral blood flow.[14]

CONCLUSIONS

1. A significant decrease in the fusion frequency of flicker occurs in patients suffering from essential hypertension as compared with healthy adults. This defect is greater than can be accounted for by hospitalization and by the difference between the mean ages of the groups studied.

2. The response of fusion frequency of flicker to graded anoxia in hypertensive patients and normal individuals is the same.

3. The depressed fusion frequency of flicker in hypertensive patients is, therefore, probably attributable to organic changes in the retinocortical system and does not result from marginal ischemic anoxia of this system or from vasospasm. Consequently, it is unlikely that studies of fusion frequency of flicker responses will aid in the detection of other vasospastic states or the delineation of "vascular hypertonus."

4. The narrow range of the difference between normal and patient groups and the stability of fusion frequency of flicker in the presence of anoxia in both indicate that fusion frequency of flicker cannot be used as a measure of latent hypertensive cerebrovascular disease.

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DRUG EFFECTS IN WOLFF-PARKINSON-WHITE SYNDROME

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SINCE Wolff, Parkinson, and White[1] described the electrocardiographic pattern which they termed bundle branch block with short P-R interval, extensive investigations of this syndrome have been made. Pre-excitation of the ventricular musculature through an accessory atrioventricular muscular pathway (such as the bundle of Kent) is the most widely accepted explanation for the syndrome of anomalous atrioventricular excitation. However, all investigators are not in complete agreement on this concept. Other hypotheses that have been suggested are: true bundle branch block; increased conductivity of one bundle branch; excitation of an ectopic focus in the ventricle by auricular contraction; fusion of a ventricular premature contraction and a normally conducted beat; depolarization of both ventricles through bilateral aberrant pathways, thus by-passing the bundle of His completely.

Various investigators have studied the WPW syndrome* by different methods. These consist of: (1) analysis of routine standard and unipolar electrocardiograms[2]; (2) intracardiac leads[3,4]; (3) mechanical stimulation of the endocardium during cardiac catheterization[10]; (4) esophageal leads[2,3]; (5) experimentally short-circuiting normal atrioventricular conduction by picking up and amplifying auricular action potentials and transmitting them to the ventricles, thus simulating aberrant muscular atrioventricular pathways[5]; (6) histologic study of hearts from known cases of WPW syndrome[6]; (7) analysis of relation between electrical and mechanical events as determined by simultaneous recordings of the electrocardiogram, venous and arterial pulse curves, intracavity and intra-arterial pressures, and electrokymograms,[7] and (8) study of drug effects.[8]

Most investigators agree that the electrocardiographic pattern of the WPW syndrome is due to early excitation of part or all of either ventricle, and normal depolarization of the remainder of the ventricular musculature. The prematurely depolarized ventricular musculature may be activated by an aberrant bundle bridging auricle and ventricle, or possibly by some other mechanism such as an irritable ectopic focus in either ventricle which is discharged by auricular activity. The electrical manifestation of this early ventricular depolarization has been termed the "delta wave."[9] In the electrocardiogram it appears as a slurring on the ascending limb of the R wave, or as a distinct deflection

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*WPW syndrome will be used as an abbreviation for Wolff-Parkinson-White syndrome.

replacing the normal P-R segment, thereby widening the QRS complex and shortening the P-R interval. The electrical activity of the remainder of the ventricular musculature, depolarized later via normal pathways, is summated with the delta wave and can often be distinguished in most leads.

If the final pattern of the QRS complex in the WPW syndrome results from fusion of excitation waves produced by impulses conducted through (1) an aberrant muscular pathway and (2) the normal junctional tissues of the atrioventricular node, then the selective action of different drugs on these pathways might be expected to produce definite alterations in the resultant QRS pattern. By the administration of drugs which have a major effect on the muscular pathway (quinidine), and of drugs which effect primarily the atrioventricular node (vagomimetic and vagolytic agents), we have attempted to vary the contributions of each of the above pathways to the final QRS pattern.

EFFECTS OF QUINIDINE ADMINISTRATION (MUSCULAR DEPRESSANT)

D. S., a case of WPW syndrome of the right bundle branch block type (Fig. 1) with no evidence of organic heart disease, was given 0.65 Gm. quinidine sulfate orally, and serial electrocardiograms were taken. Transitional changes toward a normal QRS pattern were noted before complete reversion, which occurred within ninety minutes.

Sixty minutes after the administration of quinidine (Fig. 2,*B*), the S wave in Lead I had become less negative, indicating a shift toward the normal QRS vector. In Lead II the delta wave comprised less than one-half of the ascending limb of the R wave, whereas in the control tracing (Fig. 2,*A*), before quinidine administration, it occupied the entire ascending limb. The voltage of the QRS complex in Lead III decreased toward the normal. The P-J interval* was 0.255 second as compared to 0.245 second in the control tracing.

A tracing (Fig. 2,*C*), taken ninety minutes after ingestion of quinidine, reveals conversion to a normally conducted pattern. In Fig. 2,*D*, recorded four hours after quinidine administration, the WPW pattern recurs, and as in Fig. 2,*B* the complexes are transitional, indicating a persistence of quinidine effect.

EFFECTS OF ATROPINE ADMINISTRATION (VAGOLYTIC SUBSTANCE)

Atropine sulfate, gr. 1/150, was administered subcutaneously to the same patient (D. S.) and serial tracings were obtained.

A tracing taken fifteen minutes following atropine administration (Fig. 3,*B*) revealed transitional changes which closely resembled those that were obtained following quinidine, that is, the S wave had become less negative in Lead I, and the delta wave occupied a smaller proportion of the ascending limb of the R wave in Lead II, which indicated a shift toward the normal QRS vector. However, it should be noted that the P-J interval had decreased from 0.24 second in the control (Fig. 3,*A*) to 0.22 second following atropinization, whereas following quinidine administration the P-J interval showed a slight increase in duration.

*P-J interval is measured from onset of P wave to termination of QRS complex.

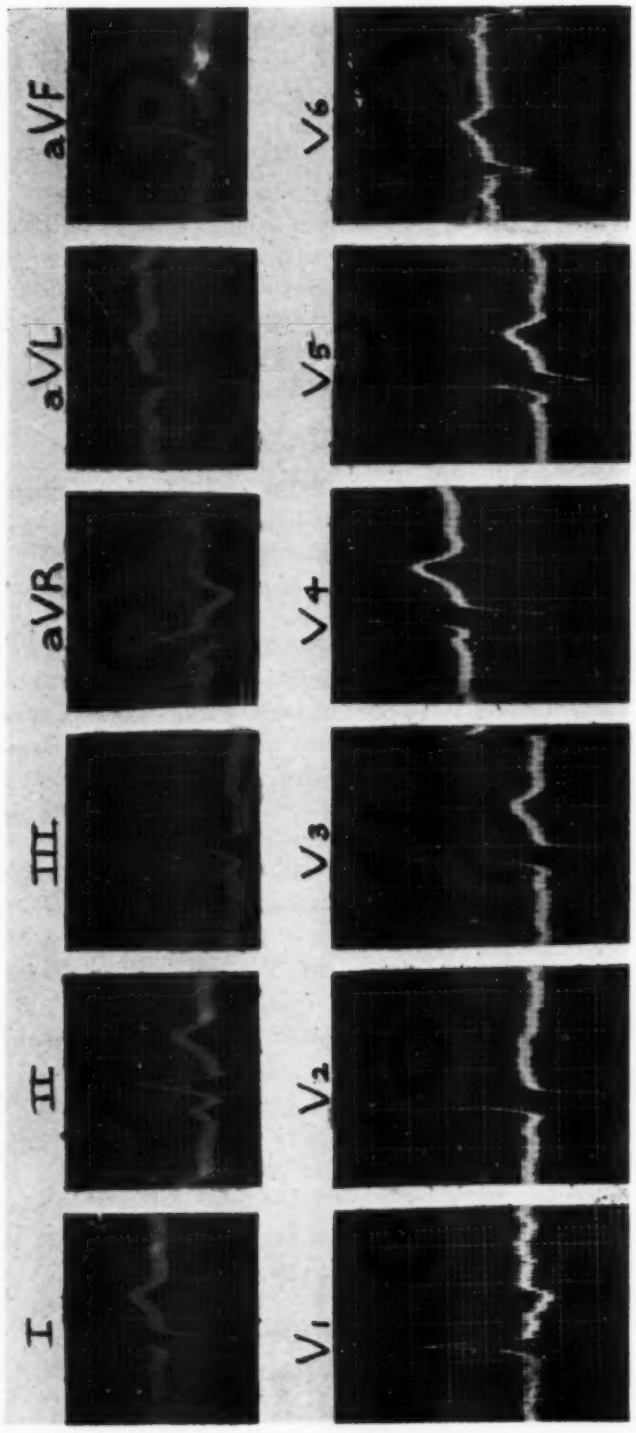

Fig. 1.—Electrocardiogram of patient D. S. showing Wolff-Parkinson-White syndrome. (All leads shown in Figs. 1-6 are Lead II.)

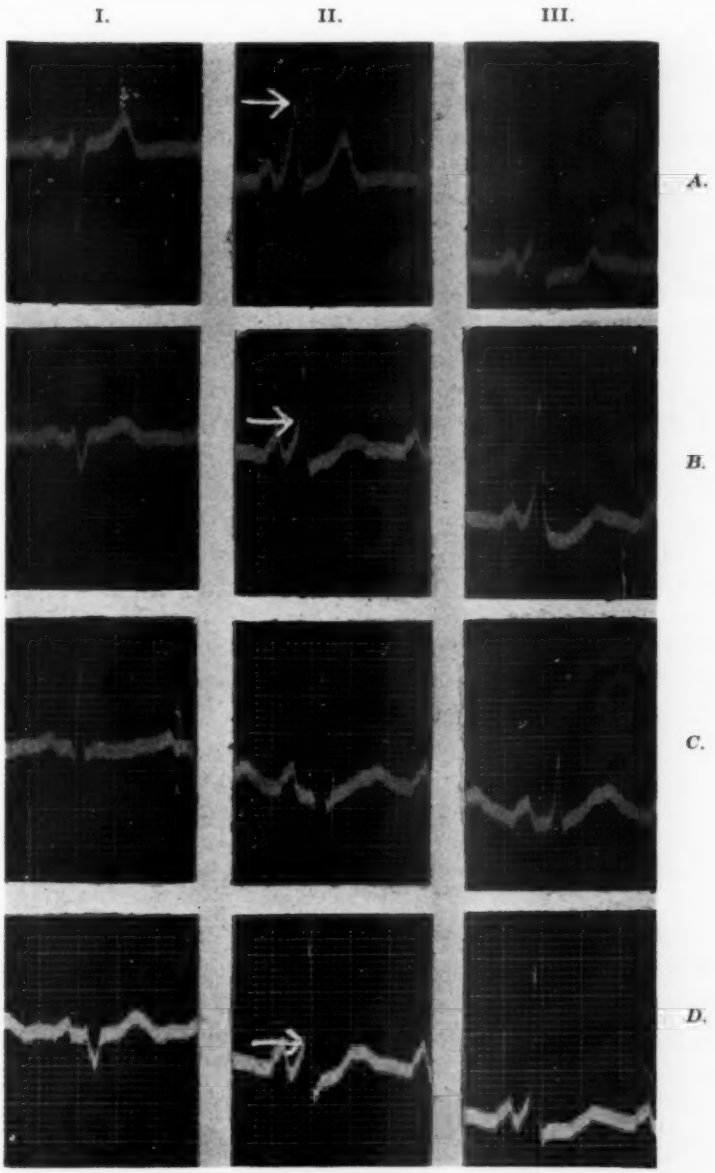

Fig. 2.—Transitional effects following quinidine administration (patient D. S.). Arrow indicates height of delta wave.

A, Control electrocardiogram before quinidine showing Wolff-Parkinson-White syndrome.

B, Sixty minutes following quinidine. Note transitional shift toward normal QRS configuration: Lead I S wave shallower; Lead II, delta wave smaller.

C, Ninety minutes following quinidine: reversion to normal conduction.

D, Four hours following quinidine: recurrence of Wolff-Parkinson-White syndrome with transitional QRS complexes as in *B*.

DISCUSSION OF QUINIDINE AND ATROPINE EFFECTS

Analysis of the transitional electrocardiographic patterns which occur following the administration of quinidine and of atropine reveals the following significant data: (1) atropine and quinidine produce transitional QRS complexes of remarkably similar configuration; (2) these intermediate QRS patterns resemble more closely the normal configuration, and (3) the P-J interval (from onset of P to the end of the QRS) shows a slight increase in duration following quinidine, whereas atropine produces a definite shortening of the P-J interval.

Atropine and quinidine, which differ widely in mode of action, have each produced a QRS pattern of more normal configuration, suggesting an increase in the contribution to the QRS complex of depolarization via normal pathways. There are two major mechanisms which could produce the shift toward the normal QRS pattern (if it be true that the "final" QRS complex results from summation of excitation waves produced by competing normal and abnormal pathways):

1. Decrease in conductivity of the shunting pathway, with a consequent decrease in the extent of premature depolarization, thus permitting greater "capture" of the ventricles by normally conducted impulses. Depolarization through normal pathways produces the terminal portion of the QRS complex. Since normal depolarization is neither speeded nor delayed, the P-J interval, which measures the duration from onset of auricular activity to termination of ventricular activity, would show no significant change from the control.

2. Increase in conductivity of normal junctional tissues, allowing earlier and more complete depolarization via the normal pathways, and thereby decreasing the proportion of ventricular musculature accessible to the shunting pathway. In this instance, since conduction through normal pathways has been speeded, the termination of the QRS, produced by normal pathways, would occur earlier in relation to the onset of auricular activity, that is, the P-J interval would be shorter.

Quinidine has produced a shift from WPW pattern toward a normal QRS pattern with no significant change in the P-J interval. Thus quinidine apparently produces its effects by means of Mechanism 1 described above. The effect of quinidine on the heart is primarily that of a muscular depressant, with only negligible effect on the atrioventricular node. It has in this instance selectively depressed the aberrant muscular pathway thereby permitting greater "capture" of the ventricles by impulses conducted through normal junctional tissues. The degree of contribution of the aberrant pathway to the QRS complex decreases with increasing quinidine effect, allowing a shift toward normal (Fig. 2,*B*). When the shunting pathway is completely depressed, the ventricles are completely depolarized through normal pathways, resulting in a normal QRS complex (Fig. 2,*C*). The converse occurs with decreasing quinidine effect (Fig. 2,*D*).

Atropine has similarly caused a transitional shift toward the normal QRS complex; however, unlike quinidine, it has produced a significant decrease in the P-J interval. Thus it is probable that atropine produces its effect on the WPW complex by means of Mechanism 2 described above. Since atropine is a vagolytic drug, it affects primarily the normal junctional tissues which are under constant

vagal control; its effect on aberrant muscular tissue is negligible. By releasing vagal inhibition of the atrioventricular nodal pathways, atropine allows more rapid conduction of impulses through the normal pathways. Thus there is earlier and more complete normal depolarization of the ventricles, and less of the ventricular musculature is accessible to aberrant depolarization. The QRS configuration therefore shows a transitional shift toward the normal. Since depolarization through normal junctional tissues has been speeded by atropine, termination of the QRS complex occurs earlier in relation to auricular activity, thus shortening the P-J interval. In contrast, quinidine, with only minor effect on the atrioventricular node, has not significantly affected the time relationships of normal depolarization, so that the P-J interval remains relatively constant.

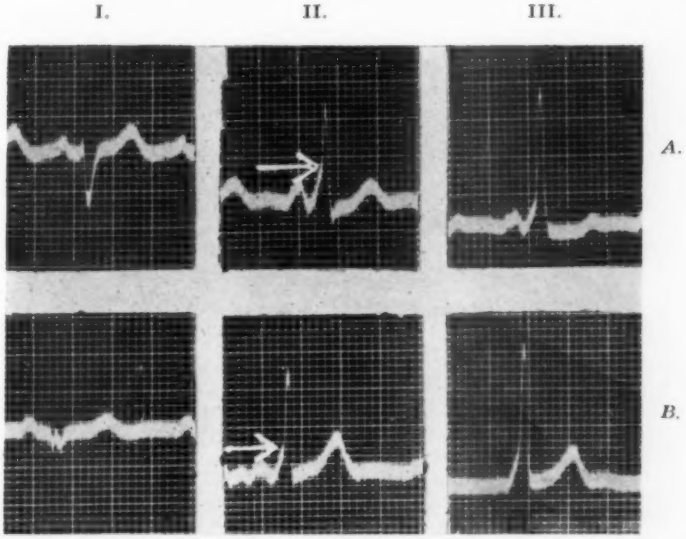

Fig. 3.—Transitional effects following atropine administration (patient D. S.). Arrow indicates height of delta wave.

A, Control electrocardiogram before atropine sh wing Wolff-Parkinson-White syndrome.

B, Fifteen minutes following atropine. Note transitional shift toward normal QRS configuration: Lead I, S wave shallower; Lead II, delta wave smaller.

POSSIBLE MASKING EFFECT OF QUINIDINE ON WPW SYNDROME

It is of importance to note that when patient D. S. first came under observation, during a bout of paroxysmal tachycardia, the diagnosis of WPW syndrome was not apparent following reversion to regular rhythm. This bout of tachycardia, like subsequent episodes, was treated with quinidine and in each instance electrocardiographic tracings obtained shortly after reversion showed normal QRS complexes. Since there was no overt evidence of pre-excitation, a diagnosis of paroxysmal tachycardia of unknown etiology was made. The correct diagnosis was further obscured by the administration of maintenance quinidine so that interval electrocardiograms also showed normal QRS complexes. It was not until a subsequent hospital admission that an electrocardiogram taken four days after the last dose of quinidine revealed a classical WPW pattern, as did all subsequent tracings taken when the patient was not receiving medication.

This experience emphasizes that the administration of quinidine can completely mask WPW syndrome as the underlying etiological factor in the production of bouts of paroxysmal tachycardia. To avoid this error, cases of paroxysmal tachycardia treated with quinidine should have an electrocardiogram recorded at least forty-eight hours after the last dose of quinidine and before maintenance dosage of the drug is begun.

EFFECTS OF PROSTIGMIN ADMINISTRATION (VAGOMIMETIC SUBSTANCE)

Prostigmin, in a dose of 2.0 mg., was administered intramuscularly to the same patient (D. S.), and serial electrocardiograms were recorded.

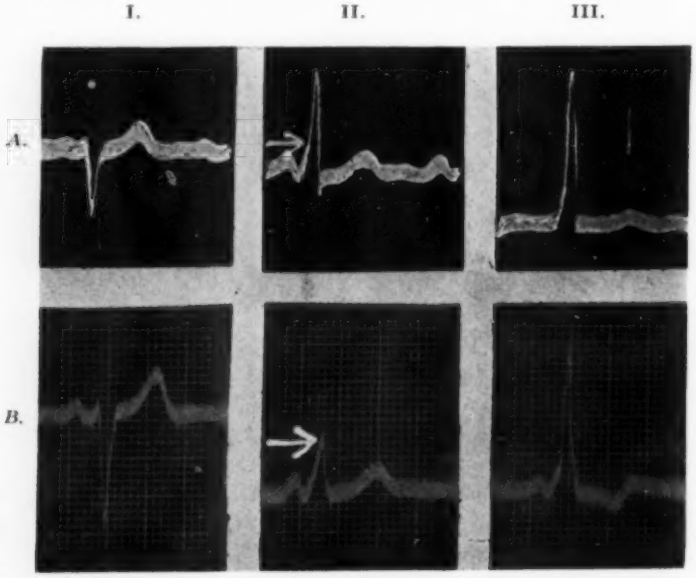

Fig. 4.—Transitional effects following Prostigmin administration (patient D. S.). Arrow indicates height of delta wave.

A, Control electrocardiogram before Prostigmin showing Wolff-Parkinson-White syndrome.

B, Sixty minutes following Prostigmin. Note transitional shift toward greater aberrancy of QRS configuration: Lead I, deeper S wave; Lead II, greater delta wave.

In a tracing taken sixty minutes after administration of Prostigmin (Fig. 4,*B*), Lead I showed an increase in negativity of the S wave as compared to the control (Fig. 4,*A*), indicating a shift away from the normal QRS vector. In Lead II the delta wave, which in the control tracing occupied approximately one-half of the ascending limb of the QRS complex, comprised the entire ascending limb of the R wave. The P-J interval has increased from 0.235 second in the control tracing to 0.25 second.

EFFECTS OF DIGITALIS ADMINISTRATION (VAGOMIMETIC SUBSTANCE)

Fig. 5 shows the effects of 2.0 mg. of Cedilanid (digitalis glycoside) administered intravenously to the same patient (D. S.). The tracing (Fig. 5,*B*), taken thirteen hours after administration showed a greater abnormality of the QRS pattern, similar to that which occurred following Prostigmin, that is, the

S wave in Lead I was more negative and the delta wave in Lead II, which in the control tracing comprised about one-half of the ascending limb of the QRS complex, occupied the entire ascending limb. The P-J interval had increased from 0.235 second in the control tracing (Lead II) to 0.25 second.

DISCUSSION OF PROSTIGMIN AND DIGITALIS EFFECTS

We have assumed that the changes in the WPW pattern following atropine administration (shift toward the normal of the QRS vector and shortening of the P-J interval) were produced by release of vagal effect on the atrioventricular node (see Mechanism 2 above). The resultant increased speed of conduction through normal pathways allows a greater contribution to the final QRS by normal depolarization. If this assumption is correct, one might expect that reverse phenomena would occur upon vagal stimulation.

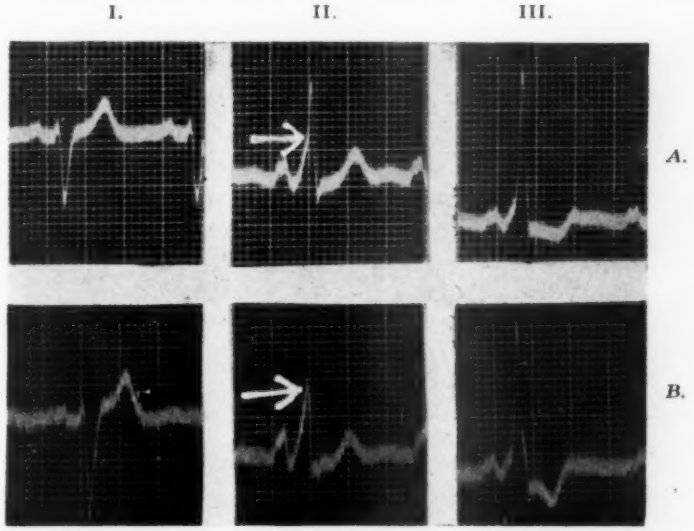

Fig. 5.—Transitional effects following digitalis administration (patient D. S.). Arrow indicates height of delta wave.

***A*, Control electrocardiogram before digitalis showing Wolff-Parkinson-White syndrome.**

***B*, Thirteen hours after digitalis. Note transitional shift toward greater aberrancy of QRS configuration: Lead I, deeper S wave; Lead II, greater delta wave.**

The results observed following the administration of Prostigmin and digitalis (vagal stimulation) confirm these expectations. These drugs produce a shift away from the "normal" (a deeper S wave in Lead I, greater delta wave in Lead II, Figs. 4 and 5) and a lengthening of the P-J interval. These effects are the reverse of the changes which occurred following atropine and are best explained by the vagomimetic effects of Prostigmin and digitalis. Vagal stimulation, by delaying conduction through the atrioventricular node, limits the extent of contribution to the QRS complex by normal depolarization. This permits greater capture of the ventricles via the earlier-acting shunting pathways and results in greater distortion (shift away from the "normal") of the final QRS complex. Since depolarization through normal junctional tissues has been delayed by Prostigmin and digitalis, termination of the QRS complex occurs later

in relation to auricular activity, thus lengthening the P-J interval. In contrast, atropine shortens the P-J interval, and quinidine has no significant effect on P-J interval (see discussion of quinidine and atropine effects).

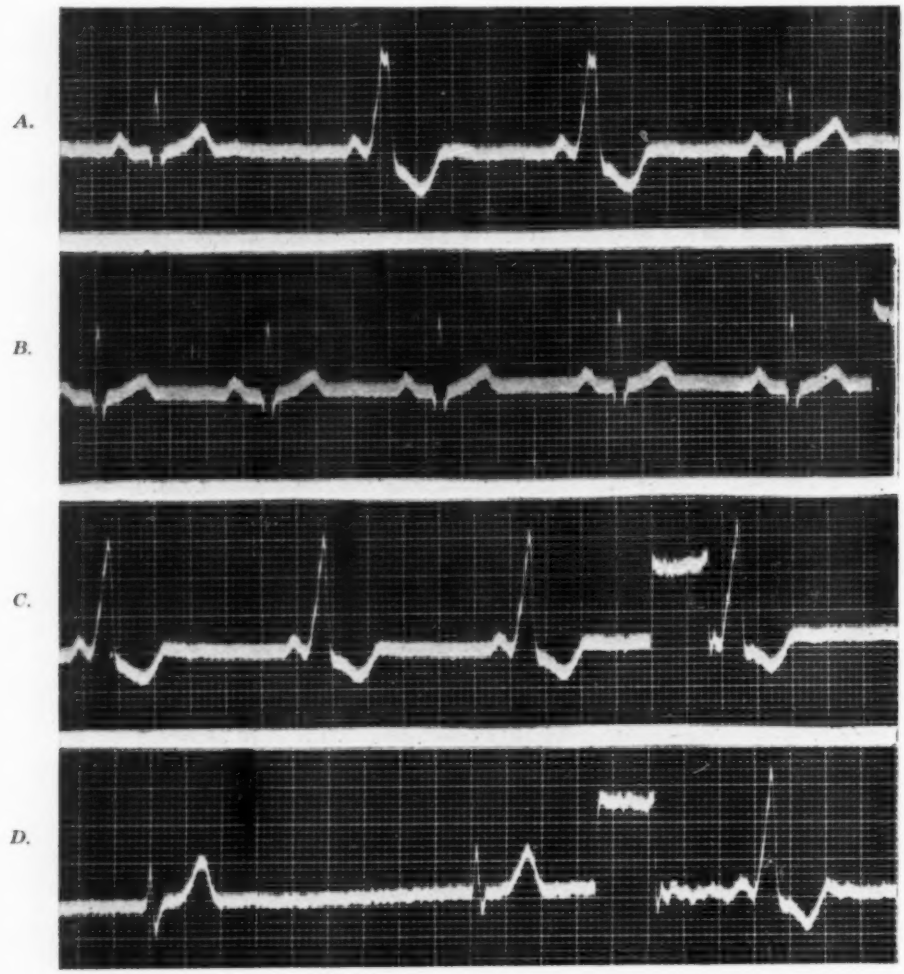

Fig. 6.—Effects of Neosynephrine intravenously in spontaneous intermittent Wolff-Parkinson-White syndrome (patient S. J.).

A, Electrocardiogram showing spontaneous intermittency of Wolff-Parkinson-White syndrome.

B, Control electrocardiogram revealing normal conduction before intravenous administration of Neosynephrine.

C, Constant Wolff-Parkinson-White conduction three minutes following 0.25 mg. Neosynephrine intravenously.

D, Nodal rhythm with normally conducted QRS complexes following 2.0 mg. Neosynephrine intravenously (see text).

EFFECTS OF NEOSYNEPHRINE

Since vagal stimulation can produce a shift away from the normal QRS configuration in subjects with constant WPW syndrome, it was felt that vagomimetic substances might be expected to produce a constant WPW pattern in cases with intermittent pre-excitation syndrome. In patient S. J., a case of spon-

taneous intermittent WPW syndrome (Fig. 6,*A*), we attempted to provoke a constant WPW pattern with various vagomimetic agents: digitalis, Prostigmin, and Neosynephrine.

The results were inconclusive following the administration of a full digitalizing dose (1.6 mg.) of Cedilanid intravenously, and following intramuscular administration of 1 mg. of Prostigmin. While there were at times sustained runs of WPW complexes following the exhibition of these drugs, a similar intermittency occurred spontaneously in control tracings.

Neosynephrine was administered intravenously in doses ranging from 0.10 mg. to 2.0 mg. In each instance, during or immediately following the injection, there occurred marked bradycardia (30 to 50 per minute) and a conversion to WPW conduction, which lasted from three to five minutes (Fig. 6,*B* and *C*). These effects were not produced by reflex autonomic changes resulting from the injection procedure per se, since intravenous administration of sterile saline on several occasions failed to alter the pulse rate or electrocardiographic pattern.

On one occasion, following the injection of 2.0 mg. of Neosynephrine intravenously, a WPW rhythm with marked bradycardia occurred. This was followed by sinus arrest, and a nodal escape rhythm (Fig. 6,*D*). During the period when there was an absence of initiating auricular activity the QRS complexes were of the normal configuration. With the resumption of pacemaking auricular activity (first P wave) the WPW pattern reappeared.

DISCUSSION OF NEOSYNEPHRINE EFFECTS

By means of its vagomimetic effect (note bradycardia) Neosynephrine has delayed normal conduction through the atrioventricular node thereby allowing constant pre-excitation to occur. For similar reasons, following administration of Neosynephrine, the aberrantly widened QRS complexes reveal a greater "shift toward the abnormal" when compared with those that occur spontaneously and intermittently in control records. The marked delay in atrioventricular nodal conduction has made possible a greater contribution to the QRS complex by the shunting pathway, and hence greater aberrancy. The marked vagomimetic effect of a large dose of Neosynephrine (2.0 mg.) resulted in sinus and auricular standstill and a return to normal-appearing QRS complexes. At the first manifestation of pacemaking auricular activity (Fig. 6,*D*) the aberrant QRS pattern recurred. This provides further evidence that the WPW syndrome is not a form of atrioventricular nodal rhythm, and that its occurrence is dependent on auricular activity preceding ventricular depolarization.

COMMENT

We have attempted in these studies to add further evidence in support of the assumptions that: (1) the short P-R interval and wide QRS of the WPW syndrome are due to premature depolarization (pre-excitation) of part of either ventricle summated with normal depolarization of the remainder of the ventricular musculature; (2) that pre-excitation is dependent on preceding auricular activity; and (3) the pre-excitation occurs via an aberrant muscular pathway bridging auricle and ventricle.

We have been able to cause marked shifts toward the normal and toward the abnormal in the appearance of the QRS complex by the administration of various drugs in two cases of WPW syndrome. It is reasonable to conclude that these diametrically opposite effects were produced by the predictable selective action of these drugs on one or the other of the bridging pathways (aberrant bundle or atrioventricular node) thereby effecting the degree of contribution of each pathway to the final QRS complex.

"Normalization" of the QRS complex was produced by both atropine and quinidine. Atropine, by its vagolytic effect on the atrioventricular node, speeds conduction through normal pathways, allowing earlier and greater capture of the ventricles by normal depolarization. Quinidine, a direct muscular depressant, apparently depresses the competing aberrant muscular pathway, limiting its contribution to the QRS complex. Either mechanism results in an increase in the contribution by the normal pathways to the QRS complex, producing a more normal-appearing (less aberrant) QRS complex. The more normal-appearing transitional QRS complexes produced by atropine and quinidine are almost identical in appearance. However, they can be differentiated by comparison of the changes that occur in the P-J interval; quinidine does not materially affect the P-J interval (action on aberrant bundle), while atropine causes definite shortening of the P-J interval (action on atrioventricular node).

Greater aberrancy of the QRS complex (shift toward the abnormal) was produced by drugs such as Prostigmin, digitalis, and Neosynephrine. These drugs, by their vagomimetic effect on the atrioventricular node, retard conduction through normal pathways, thereby allowing an increase in the contribution of the aberrant pathway to ventricular depolarization. The delay in atrioventricular nodal conduction also results in lengthening of the P-J interval.

It should be noted that these conclusions are based on results obtained in the study of one case, and may or may not apply to other cases of WPW syndrome.

Intravenous Neosynephrine, even in small doses, was effective in provoking constant WPW conduction in a subject with known paroxysmal WPW syndrome. The intermittency of pre-excitation that occurs spontaneously in such individuals is probably due to physiologic fluctuations in autonomic control of the atrioventricular node. Pre-excitation of the ventricles occurs when there is sufficient delay in atrioventricular nodal conduction so that impulses from the auricle reach the ventricles earlier via the aberrant pathway than through normal junctional tissues. In the case described, intravenous Neosynephrine, with its powerful reflex vagomimetic action, has consistently been able to depress atrioventricular nodal conduction beyond this "critical level," permitting constant pre-excitation to occur.

On one occasion, the intravenous administration of a large dose of Neosynephrine (2.0 mg.) during a run of WPW conduction produced sinus standstill and a nodal escape rhythm. The nodal complexes were all of normal configuration, and it was not until resumption of pacemaking activity by the sinus node

(P wave preceding the QRS) that WPW conduction was again manifest (Fig. 6,*D*). Previous investigators[3,8] have also noted that nodal beats occurring in known cases of WPW syndrome invariably show normal configuration of the QRS complex. Our findings provide added evidence that the aberrant QRS complex of the WPW syndrome is dependent on preceding auricular activity and is not a form of bundle branch block or nodal rhythm. These observations do not preclude the possibility that in some cases the syndrome of pre-excitation is produced by direct physical stimulation and discharge of an irritable focus in the ventricle by auricular contraction, with fusion of the resulting ventricular premature contraction and the normal beat.

It is known that individuals with WPW syndrome are predisposed to bouts of paroxysmal tachycardia. In some cases of paroxysmal tachycardia of unknown etiology it is possible that the underlying mechanism may be the presence of an aberrant pathway, which under normal circumstances is nonfunctioning. It might be revealing to subject a series of cases of functional paroxysmal tachycardia to a test of intravenous Neosynephrine following reversion to regular sinus rhythm, in an attempt to demonstrate a latent shunting pathway as the possible etiological factor.

The normalizing effect of quinidine on the WPW syndrome may be responsible for masking the etiological role of this syndrome in cases of paroxysmal tachycardia. This masking effect of quinidine was noted in one of our patients, D. S., in whom recurrent bouts of supraventricular tachycardia were interrupted by the administration of quinidine. On each occasion, electrocardiograms taken shortly after reversion to regular sinus rhythm revealed normal QRS complexes (with persistent quinidine effect on the electrocardiogram). Tracings taken while the patient was on maintenance dosage of quinidine also showed normal QRS complexes. During a subsequent hospital admission for tachycardia, a tracing recorded four days after the last dose of quinidine showed the classical WPW pattern. Only then did it become apparent that the WPW syndrome was the underlying factor in the patient's repeated attacks of tachycardia. To avoid the masking effect of quinidine, it is advisable that cases of paroxysmal tachycardia treated with this drug should have an electrocardiogram recorded at least forty-eight hours after the last dose of quinidine, and before maintenance dosage is begun.

SUMMARY

The effects of various drugs on the electrocardiographic pattern of two cases of WPW syndrome were studied:

1. A vagolytic substance, atropine, produced a transitional shift toward the normal (lesser aberrancy) in the configuration of the QRS complex, with a decrease in the P-J interval.

2. A muscular depressant, quinidine, produced a transitional shift toward the normal (lesser aberrancy) in the configuration of the QRS complex, with no significant change in the P-J interval.

3. Vagomimetic drugs, Prostigmin, digitalis, Neosynephrine, produced a transitional shift toward the abnormal (greater aberrancy) in the configuration of the QRS complex, with an increase in the P-J interval.

4. A vagomimetic substance, Neosynephrine intravenously, consistently produced constant WPW conduction in a case of spontaneous intermittent WPW syndrome.

5. The masking effect of quinidine on WPW syndrome as the etiological factor in paroxysmal tachycardia has been described.

6. The theoretical implications of these findings have been discussed.

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CLINICAL DIURETIC STUDIES ON THREE NEW MERCURIAL COMPOUNDS

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ORGANIC mercurial compounds exhibit a wide range of diuretic potency.[1] Despite the great margin of safety of most of the compounds in common use, new ones are being synthesized which promise to have greater diuretic potency with less toxicity. Evaluation in the laboratory has indicated that three new compounds, 3-chloromercuri-2-methoxypropylurea (1347Ex), 3-carboxymethylmercaptomercuri-2-methoxypropylurea (1353Ex), and 3-(*a*-carboxyethylmercaptomercuri)-2-methylpropylurea (1431Ex), have three to four times the diuretic potency of meralluride (Mercuhydrin).[2] After intravenous administration, mercury excretion rates are equivalent to meralluride.[2] For these reasons, clinical evaluation was indicated. The following study is a clinical appraisal of these drugs when administered intramuscularly to patients with cardiac failure.

METHODS

One hundred fifty-two patients were studied over a period of two years. They were divided into two series consisting of 109 patients in Series 1 and forty-three patients in Series 2. The patients in Series 1 were selected from the outpatient clinic and were used only for clinical appraisal and comparison of the diuretics under investigation. The patients in Series 2 were hospitalized patients, and detailed electrolyte studies were conducted in addition to the clinical evaluation and usual laboratory studies.

Series 1.—All of the patients in this series had been followed in the outpatient clinic for six months or more and required meralluride (Mercuhydrin) twice per week in order to remain edema free and maintain cardiac compensation. The smallest amount of Mercuhydrin necessary to maintain these patients in cardiac compensation was determined. The patients in the entire series were then divided at random into three groups, according to the experimental diuretic that they were to receive (Table I). Group 1 consisted of sixty-one patients who received 1353Ex; Group 2 consisted of twenty-four patients who received 1431Ex; and Group 3 consisted of twenty-four patients who received 1347Ex. As far as could be determined, the previous response to Mercuhydrin and the severity of

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TABLE I. EFFECTIVENESS OF THREE DIURETICS WHEN ADMINISTERED IN VARYING DOSAGES CONTAINING AMOUNTS OF MERCURY EQUIVALENT TO 50 PER CENT OF MERCURY CONTENT OF AMOUNT OF MERCUHYDRIN FOUND NECESSARY TO MAINTAIN SAME PATIENTS IN CARDIAC COMPENSATION

NO. OF PATIENTS	DOSE Hg (mg. B.I.W.)	DURATION THERAPY (MOS.)	NO. NOT DIGITALIZED	SEVERITY FAILURE				TOXICITY		NOT CONTROLLED		DRUG
				+	++	+++	++++	NO.	TYPE	NO.	PERCENTAGE	
40	10	2	10	12	12	12	4	None		12	30	1353Ex
12	20	3	2	2	3	4	3	1	Abdominal cramps	2	17	1353Ex
9	40	3	—	—	2	4	3	2	Muscle cramps	None	—	1353Ex
10	10	2	4	3	3	3	1	None		4	40	1431Ex
7	20	3	1	1	2	2	2	None		None	—	1431Ex
7	40	3	—	1	3	2	2	2	Muscle cramps	None	—	1431Ex
								3	Pain on injection			
10	10	2	3	3	2	3	2	None		2	20	1347Ex
8	20	3	2	—	3	3	2	1	Muscle cramps	1	13	1347Ex
								1	Pain on injection			
6	40	3	—	1	1	2	2	None		None	—	1347Ex

the cardiac disease in the three groups were equivalent. Because 1353Ex was the first available, a larger number of patients received this drug. The patients on each experimental diuretic were then further divided into three subgroups (Table I): those requiring 2 c.c. of Mercuhydrin (containing 78 mg. Hg), those requiring 1 c.c. (containing 39 mg. Hg), and those requiring 0.5 c.c. (containing 19.5 mg. Hg). The dose of each experimental diuretic depended on the patient's previously determined response to Mercuhydrin and was the amount which contained 50 per cent of the mercury that was required for maintaining the edema-free state when Mercuhydrin was used. Therefore, those patients receiving 1 c.c. (containing 39 mg. Hg) of Mercuhydrin were administered the new diuretics in amounts which contained 20 mg. Hg; those patients who required 0.5 c.c. of Mercuhydrin received the diuretics in amounts equivalent to 10 mg. Hg; and those requiring 2 c.c. of Mercuhydrin received the new diuretics in amounts equivalent to 40 mg. Hg. This 2:1 ratio was set up because of laboratory evidence which showed that the three new diuretics were about equivalent to each other but were considerably more potent (three to four times)[2] than Mercuhydrin when compared on a millimolar basis. All of the experimental diuretics were given intramuscularly twice a week. During the control studies, electrocardiograms and chest roentgenograms were taken. These were repeated at the conclusion of the study. Urinalyses and differential blood counts were also done during the control periods and repeated at monthly intervals thereafter. The therapeutic regimen for each patient was not altered except that the diuretic was changed from Mercuhydrin to the respective diuretic under study. About 20 per cent of the patients had not previously received digitalis (Table I) and did not receive it during the study. Most of the patients were on a low-salt diet. However, this is difficult to regulate in an outpatient clinic. The etiology of the cardiac failure consisted of hypertensive cardiovascular disease, arteriosclerotic heart disease, rheumatic heart disease, syphilitic heart disease, and unknown causes in six instances. The average age of the patients was 54 years.

Series 2.—The forty-three patients in Series 2 were admitted to the hospital for more complete studies, including water and electrolyte excretion. The majority of these patients were already partially treated when the study of the new diuretics was undertaken. This was necessary since seriously ill patients could not be maintained without therapy while control studies were being carried out. However, more than one-half of them exhibited peripheral edema, pulmonary edema, and increased venous pressure. All but twelve of the forty-three patients were on a low-salt diet (less than 2 Gm.). Activity in the ward was not limited except for the more severe cases. Fluid intake was not restricted. At the time each study was started, control observations were made, which included clinical evaluation, body weight, complete blood count, urinalysis, electrocardiogram, and chest roentgenogram. These were repeated at appropriate intervals during and upon completion of each study. Urine was collected over successive 24-hour control periods for at least three days and analyzed for total sodium and potassium. When the control values for sodium and water excretion during successive 24-hour periods seemed well stabilized, the diuretic was administered at 7:00 A.M.

Urine, collected over three or four successive 24-hour periods, was then analyzed for sodium and potassium as during the control studies. This was called one course of therapy. Each patient received approximately five such courses of treatment. Thirteen patients received 1353Ex; ten received 1347Ex, and twenty received 1431Ex. The diuretic effects of the three new mercurials were compared with each other as well as with meralluride. When the patients had completed the experimental diuretic study, they were given meralluride (1 c.c.). At least three days of control studies were used before the latter was administered, but the majority of the patients had previously been controlled with the new diuretics.

RESULTS

Series 1—Outclinic patients.—Of the sixty-one patients in Group 1 who received 1353Ex, forty received the drug in amounts equivalent to 10 mg. Hg (Table I) twice a week. On this regimen twelve developed signs of increasing failure during the course of study. All of these were controlled when the dose was increased to 20 mg. Hg. Initially, twelve patients received 20 mg. Hg. On this regimen two patients developed increasing failure, but they improved when the dose was increased. Of the nine patients who were started out on 40 mg. Hg, none developed failure.

Twenty-four patients received 1431Ex. On doses equivalent to 20 and 40 mg. Hg none developed failure. However, of ten patients receiving 10 mg. Hg, four developed failure. Three of these were controlled when the dose was increased to 20 mg. In the fourth patient it was necessary to increase the dose to 40 mg. before control of the failure was achieved.

Twenty-four patients received 1347Ex. After six weeks, two out of ten patients receiving amounts equivalent to 10 mg. Hg had developed increasing failure. On 20 mg., one patient out of eight developed increasing failure which was controlled when the dose was increased. This was a patient with particularly severe mitral stenosis and aortic insufficiency. None of the patients developed failure on 40 mg. Hg.

Series 2—Electrolyte studies.—The raw data on the electrolyte studies are presented in Tables IIA to IIC. These observations are mean values and represent the average of approximately five courses of therapy (five control studies and five post-drug studies) for each patient. The average of three successive 24-hour control periods was used to obtain the individual control value for each course of treatment. The values for the individual studies after the drug represent the first 24-hour period after drug administration. Although successive 24-hour studies were usually done for four days after each injection, it was noted that the effect on sodium excretion was manifest only during the first twenty-four hours. After that, the sodium excretion was almost invariably back to control levels and frequently dropped below the control level. The only exception was 1347Ex with which increased sodium excretion was noted in a few instances as long as forty-eight hours after the drug. A statistical summary of the electrolyte studies on the diuretics is presented in Table III. There was an increase of total sodium after the drug for all of the diuretics studied. This was due to an in-

TABLE II A. EFFECT OF DIURETIC NUMBER 1353Ex* ON WATER, SODIUM, AND POTASSIUM EXCRETION

CASE NO.	DIAGNOSIS	Na Gm./24 HR.				Na mg./C.C.				K Gm./24 HR.				URINE C.C./24 HR.			
		C	D	INC.	%	C	D	INC.	%	C	D	INC.	%	C	D	INC.	%
1	ASHD	0.34	2.34	2.00	592	0.51	4.29	3.78	742	0.80	1.39	0.59	74	665	588	− 77	−12
2	ASHD	0.62	3.25	2.63	424	0.80	2.32	1.52	190	1.23	2.06	0.83	67	851	1387	536	63
3	HHD	0.56	2.53	1.97	353	0.69	1.28	0.59	86	1.25	2.87	1.62	129	832	2000	1168	140
4	RHD	1.69	6.00	4.32	256	1.27	2.00	0.73	58	2.54	3.20	0.66	26	1331	3000	1669	125
5	HHD	0.71	1.98	1.28	181	0.25	0.53	0.28	112	0.59	1.60	1.01	171	2640	3740	1100	42
6	ASHD	0.71	2.45	1.74	246	0.54	0.41	−.13	−24	1.52	3.64	2.12	139	1272	6125	4853	381
7	ASHD	1.16	1.79	0.64	55	0.55	0.70	0.15	27	1.98	5.87	3.89	196	2100	2550	450	21
8	RHD	1.98	8.05	6.08	307	1.32	2.77	1.45	110	1.08	0.92	−.16	−15	1481	2887	1406	95
9	HHD	8.32	10.23	1.91	23	4.06	3.72	−.34	− 8	1.55	1.73	0.18	12	2050	2750	700	34
10	ASHD	0.53	2.95	2.42	460	0.74	1.54	0.80	108	1.05	3.11	2.07	197	656	1875	1219	186
11	ASHD	0.47	1.27	0.80	173	0.53	0.77	0.24	45	1.14	1.92	0.78	69	896	1542	646	73
12	HHD	0.49	3.24	2.75	558	0.44	1.21	0.77	175	0.89	3.87	2.98	334	1201	2725	1524	127
13	RHD	0.38	4.05	3.67	955	0.37	1.63	1.26	340	0.93	3.66	2.73	292	1063	2458	1395	130
Mean				2.47	352			0.85	150			1.49	130			1276	108
Standard deviation				1.44				0.94				1.11				1130	
P value between		0.1 & 0.2				0.3 & 0.4				0.2 & 0.3				0.2 & 0.3			

*Dose was the amount of diuretic containing 40 mg. Hg given intramuscularly.

Key:

C — Control
D — After diuretic
Inc. — Increase
ASHD — Arteriosclerotic heart disease
HHD — Hypertensive heart disease
RHD — Rheumatic heart disease
SHD — Syphilitic heart disease

TABLE II B. EFFECT OF DIURETIC NUMBER 1431Ex* ON WATER, SODIUM, AND POTASSIUM EXCRETION

CASE NO.	DIAGNOSIS†	Na Gm./24 HR.				Na mg./C.C.				K Gm./24 HR.				URINE C.C./24 HR.			
		C	D	INC.	%	C	D	INC.	%	C	D	INC.	%	C	D	INC.	%
28	SHD	1.32	3.92	2.60	197	0.66	1.18	0.52	79	1.58	1.70	0.12	7	2268	3282	1014	45
29	ASHD	3.50	2.25	−1.25	−36	1.50	0.56	−0.94	−63	1.06	4.00	2.94	277	2325	4050	1725	74
30	HHD	1.30	3.55	2.25	173	0.51	1.34	0.83	163	2.28	2.73	0.45	20	2550	2650	100	4
31	ASHD	0.55	1.82	1.27	231	1.22	2.20	0.98	80	0.29	0.69	0.40	138	450	825	375	83
32	ASHD	0.95	5.27	4.32	457	0.84	1.88	1.04	124	1.34	1.00	−0.37	−27	1075	2475	1400	130
33	SHD	1.54	5.97	4.43	288	0.83	1.99	1.16	140	1.92	4.58	2.67	139	1725	3000	1275	74
34	RHD	3.06	10.43	7.37	241	1.53	2.82	1.29	84	2.04	2.17	0.13	6	2000	3700	1700	85
35	RHD	3.01	8.30	5.30	176	1.28	2.24	0.96	75	1.83	1.03	−0.80	−43	2275	3700	1425	63
36	ASHD	1.80	1.82	0.02	1	1.52	0.40	−1.12	−74	0.97	2.16	1.19	122	1037	1600	563	54
37	ASHD	1.08	4.93	3.85	36	0.35	1.03	0.68	194	2.18	4.54	2.36	108	3070	4788	1718	56
38	SHD	0.51	0.92	0.41	80	0.76	1.23	0.47	62	1.40	0.60	−.80	−57	675	750	75	11
39	RHD	0.83	1.99	1.15	139	0.73	1.04	0.31	42	1.05	1.68	0.63	60	1367	1900	533	39
40	HHD	2.79	9.66	6.88	247	3.28	3.04	−0.24	−7	0.61	0.86	0.24	40	850	3175	2325	274
41	HHD	2.40	7.46	5.06	210	1.46	2.40	0.94	64	2.46	1.93	−0.53	−21	1682	3106	1424	85
42	ASHD	0.68	2.00	1.31	191	0.71	1.01	0.30	42	1.98	2.13	0.15	8	1006	1906	900	89
43	HHD	0.49	1.44	0.95	194	0.43	0.80	0.37	86	1.32	1.49	0.17	13	1188	1800	612	52
44	RHD	1.21	1.23	0.02	2	0.68	1.08	0.40	59	1.77	1.03	−0.74	−42	1769	1250	−519	−29
45	ASHD	0.62	2.67	2.04	327	0.51	1.55	1.04	203	1.40	1.61	0.20	14	1212	1825	613	50
46	HHD	0.50	2.38	1.88	372	0.81	1.59	0.78	96	0.96	3.96	3.00	313	625	1500	875	140
47	SHD	0.76	2.10	1.33	174	0.62	1.39	0.77	124	1.48	1.56	0.08	5	1227	1466	239	19
Mean				2.56	185			0.53	79			0.58	54			919	70
Standard deviation				2.30				0.63				1.19				693	
P value between		0.2 & 0.3				0.4 & 0.5				less than 0.5				0.2 & 0.3			

*Dose was the amount of diuretic containing 40 mg. Hg given intramuscularly.
†See Table IIA for key to abbreviations.

TABLE II C. EFFECT OF DIURETIC NUMBER 1347E* ON WATER, SODIUM, AND POTASSIUM EXCRETION

CASE NO.	DIAGNOSIS†	Na Gm./24 HR.				Na mg./C.C.				K Gm./24 HR.				URINE C.C./24 HR.			
		C	D	INC.	%	C	D	INC.	%	C	D	INC.	%	C	D	INC.	%
48	HHD	1.68	4.40	2.72	162	0.93	1.44	0.51	55	1.82	2.74	0.92	50	1825	3300	1475	81
49	HHD	1.41	5.79	4.38	311	0.56	1.62	1.06	189	2.57	2.85	0.29	11	2537	3575	1038	41
50	ASHD	1.61	2.71	1.10	69	1.17	1.42	0.25	21	1.69	2.09	0.40	23	1418	1900	482	34
51	RHD	2.67	4.37	1.70	64	0.92	1.04	0.12	13	3.55	4.15	0.60	17	2900	4200	1300	45
52	ASHD	0.43	2.85	2.42	567	0.42	0.95	0.53	126	0.94	3.21	2.27	240	1006	3000	1994	198
53	SHD	0.83	2.30	1.47	178	0.43	1.13	0.70	163	1.58	1.78	0.20	13	1912	2025	113	6
54	ASHD	0.50	2.79	2.29	458	0.52	0.98	0.46	88	1.24	2.83	1.69	136	960	2850	1890	197
55	?	0.98	2.44	1.46	149	0.60	1.14	0.54	90	1.62	2.10	0.48	30	1625	2140	515	31
56	HHD	0.85	2.98	1.13	133	0.58	1.42	0.84	145	2.31	2.91	0.60	26	1460	2100	640	44
57	ASHD	1.54	3.68	2.14	139	1.16	1.52	0.36	31	—	—	—	—	1326	2420	1094	82
Mean				2.08	222			0.54	92			0.83	61			1054	76
Standard deviation				0.93				0.26				0.66				591	
P value between		0.05 & 0.1				0.05 & 0.1				0.2 & 0.3				0.1 & 0.2			

*Dose was the amount of diuretic containing 40 mg. Hg given intramuscularly.
†See Table IIA for key to abbreviations.

creased urine volume as well as to an increased concentration per unit volume of urine. The increase in 24-hour potassium excretion was rather marked in some instances but in general was not a constant response to the diuretics.

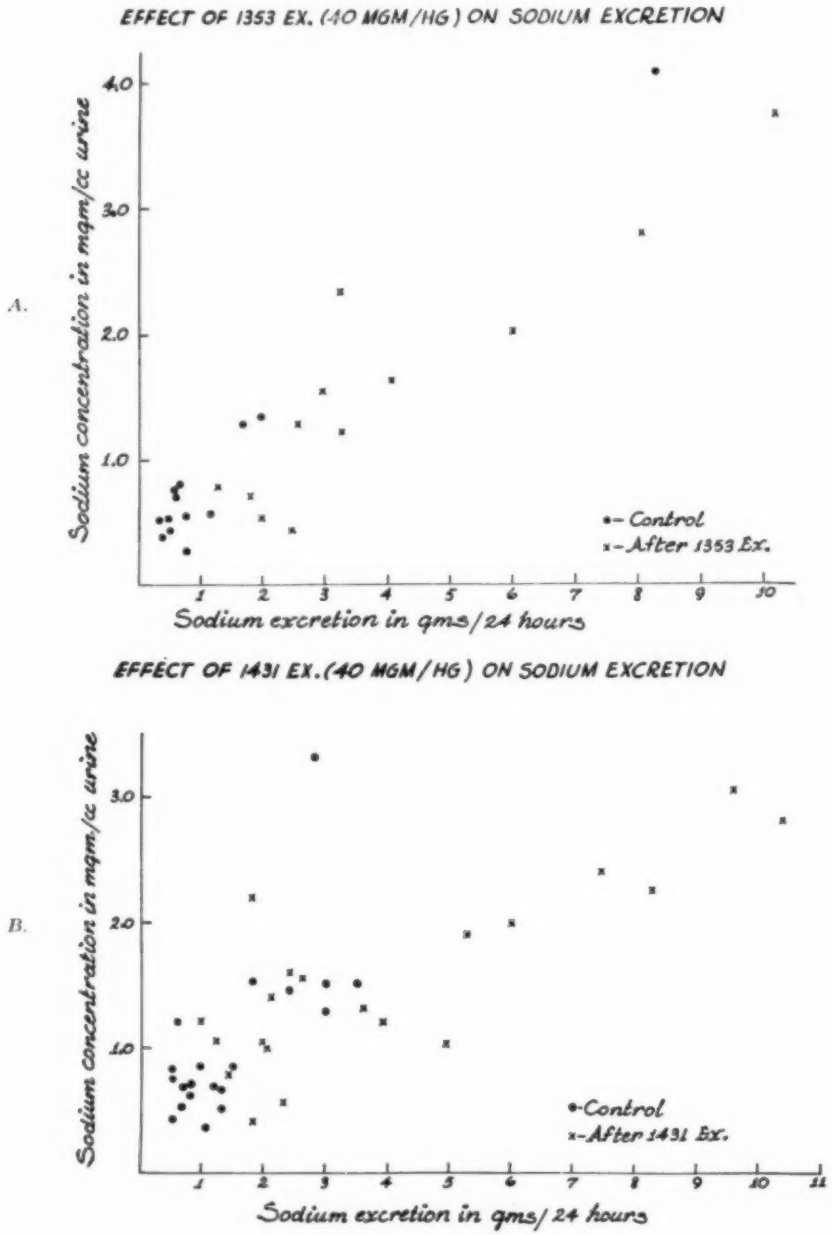

Fig. 1.—*A-D*, The twenty-four hour excretion rate of sodium is plotted against the concentration of sodium per c.c. of urine. • represents the control value. x represents the values obtained after one of the diuretics.

A, Response to 1353Ex (40 mg. Hg).

B, Response to 1431Ex (40 mg. Hg).

It is noteworthy that of the three experimental diuretics studied the effect on sodium and water excretion was most significant after 1347Ex. This is manifest in both a more significant increase in total sodium excretion and in the increased concentration of sodium per cubic centimeter of urine. The effect on water excretion is consequently not so significant as the effect on sodium excretion.

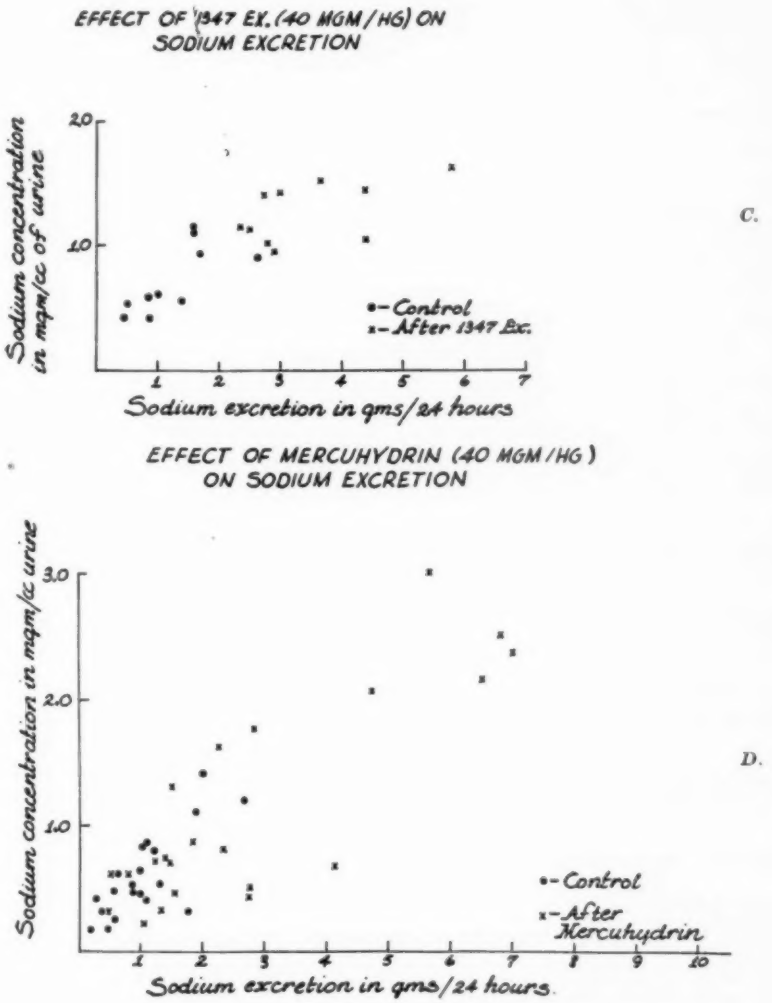

Fig. 1 (cont'd).—
C, Response to 1347Ex (40 mg. Hg).
D, Response to Mercuhydrin (40 mg. Hg).

None of the patients in this study (Series 1 and 2) presented symptoms or signs of serious toxicity (Table I). There was no demonstrable effect on the cardiovascular or on the hematopoietic system. Although albuminuria was

noted from time to time during the study, this had been noted just as frequently during the control studies. There was no other evidence of renal damage secondary to the diuretics. Muscle cramps were seen after all the diuretics in a few patients (Table I). In each instance, similar complaints had been elicited when the patients were receiving Mercuhydrin during the control studies. If the drugs were given subcutaneously, pain was quite frequent. Preparation 1347Ex seemed to be the chief offender in this respect.

DISCUSSION

Series 1—Outclinic patients.—From the observations over a three-month period on the outclinic patients, one would conclude that the three diuretics under observation were more effective than Mercuhydrin if mercurial content is used as the basis of comparison. It appears that with the larger doses of the drugs the three new diuretics possess two or more times the diuretic potency of Mercuhydrin. This was apparent (the patients were well controlled when the larger doses of the diuretics were used) despite the fact that the amount of mercury administered was only one-half of that which was found necessary with Mercuhydrin. However, when smaller doses of the new diuretics were given (equivalent to 10 and 20 mg. Hg), this same ratio of greater diuretic potency did not exist. As a result, a number of the patients developed increasing failure on a dose equivalent to 10 mg. Hg; whereas previously they were well controlled on 0.5 c.c. Mercuhydrin (equivalent to 20 mg. Hg). When the dose of the new diuretics was increased to amounts equivalent to the mercury content of the Mercuhydrin required, then control was again established. This is probably an expression of the dosage response curve of most drugs[3] and indicates that a threshold dose of mercury must be delivered to the kidney for ionization[4,5] before an effective diuretic response is established. The smallest dose for Mercuhydrin that is consistently effective appears to be 0.5 c.c. (20 mg. Hg).[3] It apparently is about the same for the three new compounds under investigation, since, when amounts less than this are administered, a number of the patients developed increasing failure, despite the fact that they had previously been controlled on 0.5 c.c. of Mercuhydrin. Had the studies been continued over a longer period of time, more of the patients on these smaller doses of the new diuretics might have developed failure.

In patients who are relatively unresponsive to Mercuhydrin and require larger doses of the drug, there appears to be a discrepancy between the amount of Mercuhydrin and the amount of the newer diuretics required. Patients requiring 2 c.c. of Mercuhydrin (equivalent to 80 mg. Hg) appeared to do just as well on the new diuretics in amounts equivalent to only 40 mg. Hg. We would deduce that, although the threshold dose for Mercuhydrin and the new diuretics is about the same, the slope of the dosage response curve is greater with the latter.

Series 2—Electrolyte studies.—By observations on the data in Tables IIA to IIC, it is evident that the three diuretics being investigated increase sodium excretion. This is reflected in an increase in concentration per unit volume

(Fig. 1,*A-D*) of urine as well as in the increase in the amount of urine. This increase lasted up to twenty-four hours and is quite similar to that of other mercurial diuretics.[5-8] It suggests that the primary effect of these drugs is on the tubular reabsorption of salt, resulting in an obligatory loss of water. There is no evidence from our data to indicate whether this is due primarily to inhibition of chloride reabsorption or sodium reabsorption.[5,7,8] However, sodium is thought to be the principal ion involved in fluid retention resulting from cardiac failure.[6] In contrast to the observations after these diuretics, when cardiac failure is controlled without diuretics (bed rest and digitalis), the sodium and chloride are lost in the same concentrations as they appear in the extracellular fluid.[6,9,10] The fact that increased potassium excretion frequently was associated with the sodium diuresis after these mercurial diuretics suggests that this cation may have been carried along in combination with the chloride to replace part of the deficit created by disproportionately greater losses of chloride than of sodium ions. On the other hand, Mudge and associates[11] have found evidence to indicate that mercurial diuretics decrease potassium reabsorption directly.

TABLE III. STATISTICAL SUMMARY OF EFFECT OF THREE EXPERIMENTAL DIURETICS ON WATER AND ELECTROLYTE EXCRETION, COMPARISON WITH MERCUHYDRIN

	Na Gm./24 HR.		Na mg./C.C.		K Gm./24 HR.		URINE C.C./24 HR.		NO. OF PATIENTS
	INCREASE	STD. DEV.	INCREASE	STD. DEV.	INCREASE	STD. DEV.	INCREASE	STD. DEV.	
Table II A (1353Ex, 40 mg.)	2.47	1.44	0.85	0.94	1.49	1.11	1276	1130	13
Table II B (1431Ex, 40 mg.)	2.56	2.30	0.53	0.63	0.58	1.19	919	693	20
Table II C (1347Ex, 40 mg.)	2.08	0.93	0.54	0.26	0.83	0.66	1054	591	10
Mercuhydrin, 40 mg.	1.78	1.78	0.47	0.59	0.67	1.53	1049	1093	22

Table III indicates that, statistically, the diuretic 1347Ex is the most active drug studied. This is reflected in a greater increase in sodium per unit volume of urine as well as in total 24-hour excretion of sodium and water. However, percentage wise, the increase in the mean values was greater after 1353Ex (Tables IIA and IIC). The apparent discrepancy here is no doubt due to the more variable sodium intake in the group receiving 1353Ex and 1431Ex. This results in a large variation in sodium excretion during the control periods, which reduces the statistical significance of the changes which occur after the drugs.

The reason that Mercuhydrin does not show more of a significant change in sodium and water excretion is no doubt due to the fact that the patients were approaching "dry weight" before the Mercuhydrin was administered. However, it does indicate that Mercuhydrin did not produce a significant additional diuresis when it was administered after the experimental drugs.

The absence of local tissue reaction after intramuscular injection of 1353Ex and 1431Ex is attributable to the chemical structure and presence of the thiol group, since this combination decreases the local tissue irritability and increases absorption without affecting the diuretic potency.[5] It is of interest that 1347Ex was similarly nonirritating, although it does not have a thiol group, nor does it contain theophylline. Although these experimental diuretics are more active than Mercuhydrin when administered parenterally, they offer little advantage over mercurials in common use today. Because of pain when given subcutaneously, it was necessary to administer them intramuscularly. However, the absence of evidence of cardiovascular or renal damage or changes in the hematopoietic system indicates that these drugs are safe for clinical use.

SUMMARY

1. Three new mercurial diuretics, 3-chloromercuri-2-methoxypropylurea (1347Ex), 3-carboxymethylmercaptomercuri-2-methoxypropylurea (1353Ex), and 3-(*a*-carboxyethylmercaptomercuri)-2-methylpropylurea (1431Ex), have been evaluated on 152 patients. The drugs were given twice per week, intramuscularly, in varying doses to 109 patients in the outpatient clinic. The diuretic effects of the drugs were compared to the previous responses of the patients to Mercuhydrin.

2. In doses equivalent to 10 and 20 mg. Hg of the experimental diuretics, none offered much of an advantage over Mercuhydrin. This is apparently due to the fact that a threshold amount of mercury must be presented to the renal tubules before any diuresis results, regardless of the mercurial compound. From clinical observations this amount appears to be between 10 and 20 mg. Hg.

3. When larger doses of the experimental diuretics (equivalent to 40 mg. Hg) were administered, they appeared to have a higher order of potency than Mercuhydrin when compared on the basis of mercurial content. When evaluated on a clinical basis, this ratio was greater than 2:1 and appeared to be about the same for all of the drugs under investigation.

4. Electrolyte studies were done on forty-three hospitalized patients. After all three of the diuretics there was a marked increase in urine and sodium excretion. The concentration of sodium per unit volume of urine was also increased. Potassium excretion was increased but this was erratic.

5. Of the three experimental diuretics studied, 1347Ex exhibited an increase in sodium and water excretion of highest order of statistical significance.

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A MANNIKIN TO SIMPLIFY THE TEACHING OF CONGENITAL HEART DISEASE

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THE DEVELOPMENTS in cardiovascular surgery during the past decade have aroused a general interest in congenital heart disease. Consequently, this topic is appearing frequently in hospital teaching conferences, convention forums, and medical school lectures.

The pathology of embryologic anatomy with either malposition or maldevelopment of septae, great vessels, or cardiac chambers is responsible for the complexity of clinical findings associated with this condition. It is understandable, therefore, that a discussion of the anatomic phases of congenital anomalies also involves the physiopathologic aspects.

The presentation of this subject would indeed be difficult without the use of a diagrammatic scheme accompanying the lecture. In most instances the use of projection slides is resorted to. Obviously, this public-speaking tool has been of invaluable assistance to the medical lecturer for a considerable period of time. There is a disadvantage to this method when presenting a topic which requires considerable concentration since the visual image should be constantly in view. Unless the audience is thoroughly familiar with the nature of the lesions being presented, confusion may exist unless the slide is left in place during the discussion.

The mannikin (Fig. 1) is presented as an attempt to avoid this problem. Several advantages are evident. The nature of the lesion under discussion remains in view as long as is desired so that other projection slides may be used to elaborate on the subject. Once oriented to the basic vascular pattern, reorientation to various anomalies is not difficult.

The unit consists of a two-dimensional plastic "cutout" of the heart and great vessels, including vascular supply to the lungs. The regions of the aortic arch and the root of the aorta and pulmonary artery are removable units. The selection of a number of interchangeable pieces permits the nature of the cardiac lesion to be changed by a simple replacement maneuver.

From the Department of Radiology, St. Louis University School of Medicine.

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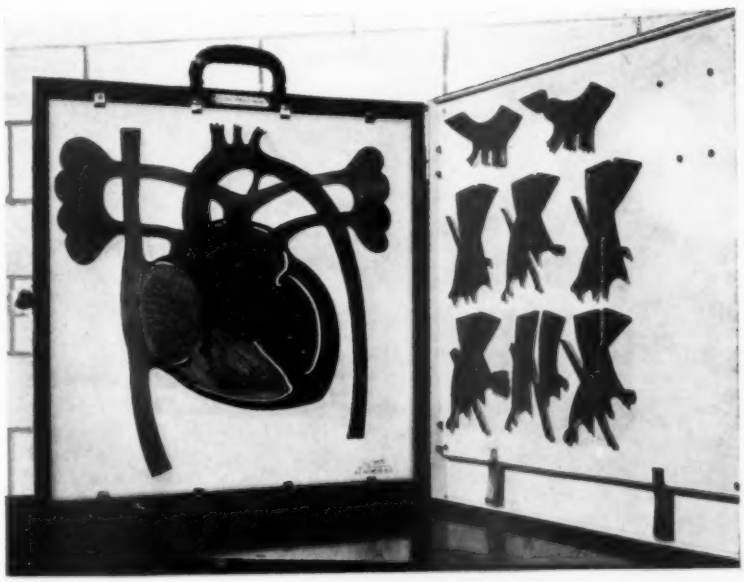

Fig. 1.—The photograph shows a persistent patent ductus arteriosus. Other replaceable inserts are seen on the cover.

The basic unit is one-fourth inch of plastic (approximately 18 inches in its longest diameter) fused to a background plate of frosted Plexiglas (20 inches × 24 inches). Light souce is two fluorescent tubes within the viewing box.

The interchangeable pieces are also of one-fourth inch plastic. Plastic pegs on the back of these pieces fit into holes aligned in the frosted Plexiglas background.

Coloring is by means of special paint available commercially especially for this purpose.

The viewing box is a self-contained unit. Its cover serves to protect the model and has carrying space for the interchangeable pieces. Its size is adequate for auditorium teaching.

Grateful acknowledgement is given to Mr. Carl Tabor for the work in plastics, and the Dick X-Ray Company for the development of the viewing box carrying case.

Clinical Reports

SCHISTOSOMAL HEART DISEASE: BILHARZIC COR PULMONALE

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SCHISTOSOMIASIS is generally not considered a cause of heart disease. No mention is made of it in most textbooks on cardiology. Recent reports,[1-3] however, have indicated that infrequently the disease may involve, indirectly, the heart, producing a striking clinical and pathologic cardiac entity. It has been suggested that this cardiopulmonary form may not be as rare as previously thought and that some of the cases reported as Ayerza's disease of unknown etiology were bilharzial.[4,5]

In the recent wars large numbers of our armed forces were exposed to schistosomiasis and many developed the disease. Also, modern methods of rapid transportation have brought all lands closer together and have made it necessary for us to become more familiar with diseases which previously had been almost entirely limited to distant places such as Egypt, South Africa, Asia, and Japan. Schistosomiasis is extremely prevalent in the above-mentioned places. A necropsy study[6] in Southern Rhodesia (1949) indicated that about 90 per cent of the adult native inhabitants of that land had schistosomiasis. In Egypt, of its 14½ million inhabitants, 60 to 70 per cent were reported infected with Schistosoma.[5] It is stated that in Puerto Rico all the islanders are presumably infected.[7] In the United States there were reports of only 22 cases up to 1926.[8] However, Symmers has recently (1951)[8] indicated that the number of cases in the United States is increasing. The disease is usually mild and few affected are incapacitated. Death is caused by the disease in only 1 to 2 per cent of the cases. The pulmonocardiac form reported[6] as rare in Southern Rhodesia is common in Egypt.[5] This distribution is difficult to understand since infection with *Schistosoma haematobium* as well as with *S. mansoni* is frequent in both places[5,6] and pulmonary involvement may be caused by either, though somewhat more frequently by *S. haematobium* due to the greater tendency to pulmonary embolism from the pelvic veins. In Southern Rhodesia about 50 per cent of the subjects with bilharzia examined by Gelfand had some lesions in the lungs at necropsy.[6] These were always in small number, scattered singly in the parenchyma with little or no tissue reaction and were not responsible for any functional disturbance. *S. haematobium* were found somewhat more frequently than *S. mansoni*. In Egypt, 33 per cent of all bilharzial disease had pulmonary involvement. In some this was extensive, causing profound effects on the pulmonary arteries and heart.

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In 2 per cent it was the cause of death in right heart failure.[5] In cases with severe pulmonary involvement there is an unusual and characteristic cardiac picture.[1]

The following case is reported because, besides adding to the small number of published cases of bilharzial heart disease, several cardiac studies are described for the first time, and to the best of our knowledge this is the first report of a case diagnosed ante mortem in this country.

CASE REPORT

A. W., a 30-year-old white rabbi, was born in Lithuania. He lived there ten years before going to Israel where he had resided for the past twenty years up to two weeks before his admission to the Beth Israel Hospital on May 13, 1951. He was married eight years ago, just before the onset of the present illness. He had no children. His mother had diabetes; his father, gall bladder disease. He knew of no blood disease in the family. He had a tonsillectomy at the age of 10 years; an attack of intestinal amebiasis six years ago. There was no history of malaria, rheumatic fever, scarlet fever or allergy, jaundice, hypertension, previous renal disease, or edema of the face or extremities. During childhood and adult life he had several medical examinations but was never informed of the presence of any cardiac abnormality until about five years ago when he was told he had heart trouble. This was diagnosed as rheumatic mitral stenosis by some examiners and congenital heart disease by others.

Present Illness.—A. W. said he was well up until about 1943. For the first time, he then noticed his urine was reddish. The hematuria was persistent and seemed to be worse in cold weather, about six hours after drinking cold drinks, after placing his hands in cold water, after a hot bath, after a long hike, and when he had been confined to bed for about two weeks. This worsening of the hematuria lasted as long as two months. It was usually associated with some generalized abdominal pain, passage of flatus, and nausea. The patient was very nervous and anxious and because of this, together with language difficulty, it was possible that some of these statements were suggested by the historian, as the admission diagnosis was hemolytic anemia. Five years ago, after a hard climb, he coughed up blood; hemoptysis recurred this winter, also after overexertion. There had been no hematemesis and no melena. He said he did not bruise easily, there was no nocturnal predisposition for red urine, and no chronic drug habit. There were no chills and fever. For several years he had had palpitation of the heart with effort, dyspnea on climbing one flight of stairs, two to three pillow orthopnea, but no ankle edema. He complained of some weakness during the past three or four years.

Physical Examination.—The patient was a well-developed, well-nourished white man, 30 years of age, who appeared neither acutely nor chronically ill, although somewhat anxious looking. His temperature on admission was 99.4°F., pulse rate 80, and respiration 20 per minute. The skin was normal, except for an old 2 cm. raised bluish-red area on the back. Examination of the eyes revealed: sclera was not icteric; pupils were equal and reacted to light and accommodation; conjunctiva had good color; there were no petechiae. Fundi revealed slight pallor of the discs, normal blood vessels, and no hemorrhages or exudates. No ptosis or proptosis was noted. In the mouth, there were several silver teeth. Papillae on the tongue were hypertrophic; the tonsils were red and large but not inflamed; the nasopharynx was slightly injected. The neck was supple; there was no adenopathy; the veins were not distended, and the trachea was in the midline. The chest was normal in shape and movements. The breasts were enlarged slightly. The lungs were clear to percussion and auscultation with the exception of an inspiratory wheeze at the right base. Râles and ronchi were not heard. The breath sounds and fremitus were normal. In the heart, the point of maximal impulse of the apex beat was in the fifth intercostal space at the midclavicular line. It was forceful and could be felt to 1 cm. lateral to the anterior axillary line in the seventh intercostal space; there was no thrill. Percussion revealed increased cardiac dullness to the right and left. The heart sounds were loud and heard all the way to the right axilla. The first sound at the apex was of moderately increased intensity; it was not followed by a murmur. The second sound was much louder and snapping in quality. The second pulmonic sound was also loud and snapping. A third heart sound was heard at the apex, about 2 to 3 cm. medial to the apex. The

rhythm was regular. The blood pressure was 120/80 mm. Hg. In the abdomen, there was no tenderness and no abnormal masses. The liver was slightly enlarged. The spleen and kidneys were not palpable. There were no scars or herniae and no tenderness at the costovertebral angles. Rectal examination showed the sphincter to be normal. No abnormal masses were present; feces were brown and well formed. The prostate felt normal. There was no cyanosis, edema, clubbing or varices in the extremities; the calf was not unduly tender on pressure; Homan's sign was negative. Dorsalis pedis pulsations were palpable. Neural examination revealed that sensation was present and normal in all modalities. There was no loss of motor power. Deep and superficial tendon reflexes were normal and symmetrical except for diminished knee jerks bilaterally.

Laboratory Findings.—The urine was yellow and frequently reddish. Specific gravity was 1.018 to 1.022; tests for albumin were 1 to 4 plus, for glucose negative. On microscopic examination the urine was frequently found loaded with red blood cells and there were occasional blood and granular casts. Spectroscopic examinations for hemoglobin were performed on several specimens of serum; all were negative. The urine after centrifuging was likewise tested for hemoglobin and the supernatent fluid was negative. The blood count showed 5.1 million red blood cells per c.mm., 15.4 Gm. hemoglobin per 100 c.c., 8,250 leukocytes per c.mm., of which 55 per cent were polymorphonuclears, 44 per cent lymphocytes, 3 per cent eosinophils, and 3 per cent mononuclears. The reticulocyte count was 0.9 per cent, platelets 220,000; there were no sickle cells. The fragility test was normal beginning at 0.50 per cent saline and ending at 0.35, the same as for the control; coagulation time was 2 minutes, bleeding time 55 seconds, prothrombin time 15.4 seconds. The Coombs test was negative. The tests for cold agglutinins in the blood were negative. Agglutination tests for the following were also negative: typhoid H and O, Salmonella, Brucella, and O.X. 19. The test for heat agglutinins in the blood at 37° C. also was negative. The erythrocyte sedimentation time was 15 mm. in one hour (Westergren). The fasting blood glucose was 90 mg. per 100 c.c.; nonprotein nitrogen, 33 mg. per 100 c.c.; blood protein, 7.28 Gm.; albumin 4.57 and globulin 2.71, giving an A/G ratio of 1.69. The blood serum cholesterol was 130 mg. per cent with esters 82 mg.; acid phosphates 1.05 and alkaline phosphatase 1.0, Bodansky units. Bilirubin was 0.78 direct, 2.55 total mg. per 100 c.c.; blood carbon dioxide combining power 22.9 meq. per liter. The venous pressure in the median basilic vein was 12 cm. of water, rising 1.5 cm. on pressure over the right upper quadrant of the abdomen. The arm-to-tongue circulation time (Decholin) was 27 seconds. The blood Wassermann, Mazzini, and Kahn tests were negative. Clearance of blood urea was 70.3 per cent of average normal function. Just prior to admission to the hospital, at the office of the urologist, a blood culture was taken and reported to contain hemolytic *Staphlococcus aureus*. Several blood cultures were taken while he remained at the hospital. Enriched media was used and the cultures were held for one to two weeks. All were sterile. He had no fever during the entire hospital period of one month; antipyretics or antibiotics were not administered. Acid-fast bacilli were not found in the urine on several tests; monilia albicans was seen in two specimens but not in the many others or in the last several specimens. Tests for occult blood in the stools were negative.

The electrocardiogram (Fig. 1) revealed marked deviation of the electrical axis to the right; angle alpha was plus 144 degrees. S_1 was 10.2 mm.; R_1, 2.0 mm.; R_3, 12.7 mm.; $Q_3 = 2.0$ mm. R in aV_R was 5.5 mm., in V_1, 15.5 mm.; S in V_6 was 18 mm. The T waves in the precordial Leads V_1 through V_6 were all inverted, as predicted by Kenawy,[3] since the right ventricle probably composed the whole anterior surface of the heart and there was right ventricular strain. The electrocardiogram suggested hypertrophy of the right ventricle and considerable clockwise rotation (electrical).

X-Ray Examination.—The pyelogram was normal. Intravenous urography, after the injection of Diodrast for the angiocardiogram, showed good visualization of both upper urinary tracts without abnormality. The teleroentgenogram indicated considerable enlargement of the heart, pulmonary arteries, and their branches (Fig. 2). On cardiac fluoroscopy the cardiac enlargement was seen to be due mainly to enlargement of the outflow tract of the right ventricle. There was extreme enlargement of the major pulmonary vessels; no enlargement of the left auricle was observed, but there was possible enlargement of the left ventricle. The aorta was small. This roentgenographic appearance was considered compatible with interatrial septal defect. The lack of prominent pulsations of the large pulmonary vessels was attributed to intrapulmonary throm-

bosis. The roentgenologist believed it difficult to make a definite diagnosis and advised taking an angiocardiogram. The clinical diagnoses were paroxysmal hemoglobinuria, amebiasis, tuberculosis of kidneys, chronic glomerulonephritis, cardiac enlargement, valvular heart disease, and hemolytic disease. (See Fig. 3.)

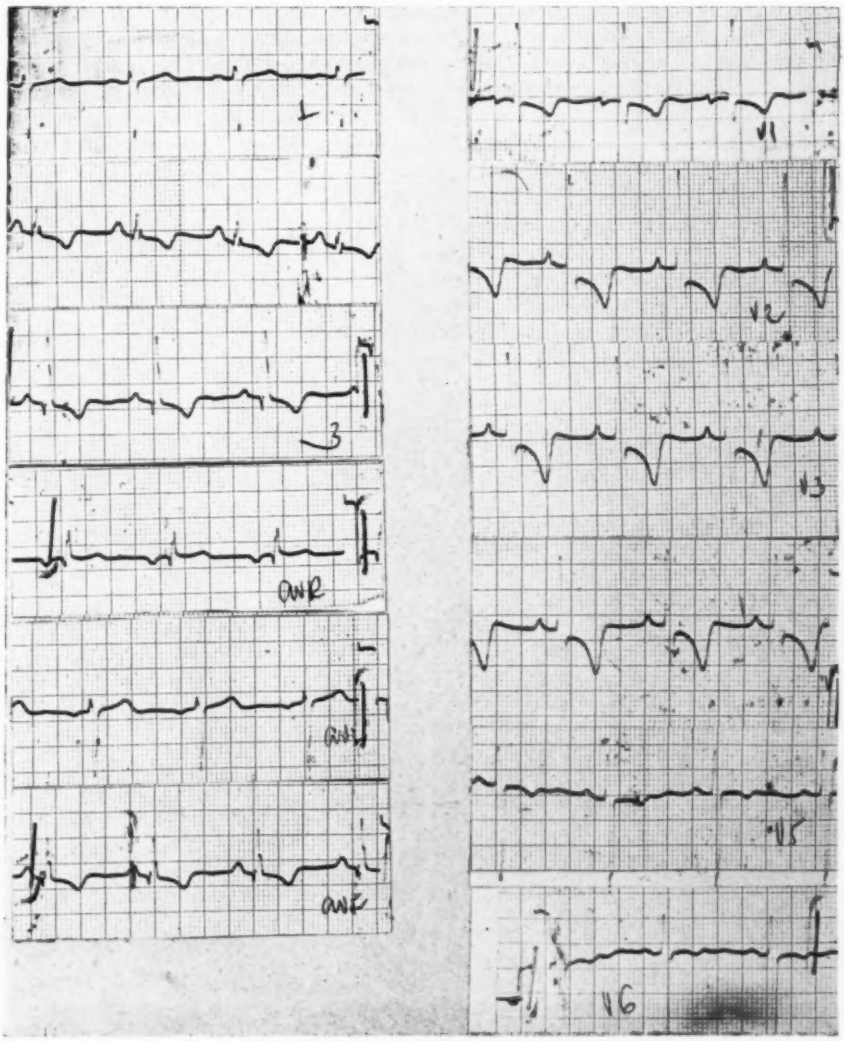

Fig. 1.—Electrocardiogram. Three standard limb leads, three augmented unipolar limb leads, and six conventional unipolar precordial leads. There is marked right axis deviation (angle alpha plus 144 degrees), considerable clockwise rotation (electrical), and electrical criteria of right ventricular strain and hypertrophy. T waves are inverted in all six precordial leads; the transitional precordial zone is to the left of V_6. S is 25 mm. in V_2 and 27 mm. in V_3.

An angiocardiogram was made on May 23, 1951, by Drs. M. Goodgold and A. Seligman (Fig. 4). It showed a normal flow of Diodrast into the right innominate vein to the superior vena cava. The right auricle and ventricle filled promptly. The interventricular septum bulged toward the left ventricle, a reverse Bernheim phenomenon, indicating increased right ventricular pressure; some enlargement of the right ventricle was likely. There was marked dilatation of the main pulmonary artery and the major and segmental branches in both lungs. Despite the long period, from the time of injection (twelve seconds), over which films were taken, at no time was any

opaque medium visualized in the aorta. There was only faint visualization of the left ventricle in the last film. The cause of this was not clear. The region of the infundibulum and valve of the pulmonary artery appeared narrow compared to the marked dilatation distal to this region. It was thought by one observer that such a narrowing might explain the delay. Some asystole following injection of the dye could account for continued opacity of the right side. There was no evidence of an intracardiac shunt and the right atrium was not dilated—evidence against atrial septal defect. A diagnosis of pulmonary stenosis with poststenotic dilatation was suggested, but the marked dilatation of the major pulmonary arteries and branches extending a considerable distance peripherally into the lung seemed greater than that observed in pulmonary stenosis.[9] It was thought that this might be caused by some obstructive lesions in the distal pulmonary arterial tree, the small pulmonary arterial radicles.

Because the patient came from the Middle East, it was thought possible that schistosomiasis with multiple emboli of eggs to the lungs might produce the condition. An excellent example of this was found in the paper by Bedford and associates.[1] The illustrated roentgenogram in their case revealed right ventricular enlargement and aneurysmal dilatation of the major pulmonary arteries, and was strikingly similar to the teleroentgenogram in our case (Fig. 2). In their case confirmation of the absence of valvular or congenital heart disease was obtained at autopsy which disclosed the presence of extensive schistosomal disease of the lungs and small pulmonary arteries responsible for the extreme cor pulmonale.

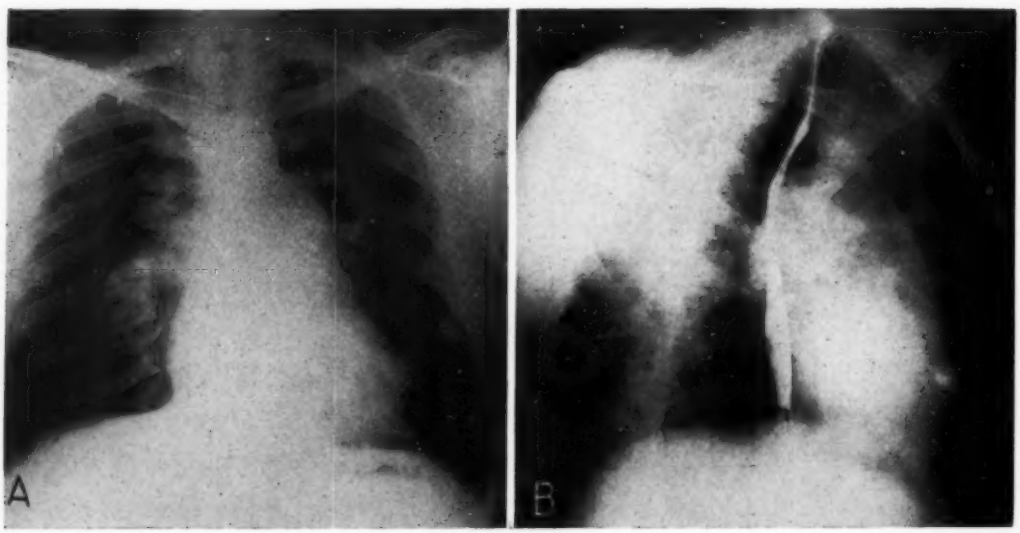

Fig. 2.—Teleroentgenogram. *A*, Marked dilatation of the pulmonary artery and its branches extending out from both right and left hilus; the cardiac apex appears rounded; lung fields pleoanemic. *B*, Right anterior oblique position with esophagram. The straight-line contour of the barium-filled esophagus at the region of the left and right atrium indicates no significant enlargement of these chambers. There is considerable indentation of the esophagram above caused by the enlarged pulmonary artery.

In our case the following additional history was obtained. About one year before the onset of hematuria, the patient had bathed in the Yarkon river which is at the outskirts of Tel Aviv in Israel. Subsequently, bathing in this river was prohibited because of the presence there of Schistosoma.

A search for ova in the patient's urine and stool was then made. On several occasions oval bodies were seen in the centrifuged urinary sediment among the many red blood cells; these were of proper size but spines were not seen and identification was uncertain. Stools were examined but ova were not found. A Fairley complement fixation test was reported as negative. At this time the patient became uncooperative, refused to allow further investigation at the hospital, and

insisted on leaving. After discharge a cystoscopy was performed at the office of the urologist to whom he originally had been referred from Israel. It revealed the bladder to be normal in appearance and catheterization of the ureters showed blood coming from both ureters.

The presumptive diagnosis of schistosomal heart disease was made on the basis of the following: (1) the history of bathing in Schistoma-infected water; (2) the onset of hematuria within about one year thereafter, and no other apparent cause for hematuria now of eight years' duration; hemolytic disease, hemoglobinuria, renal calculi and other renal disease had been carefully excluded; (3) the pulmonary and cardiac features, in particular the unique cardiac silhouette with

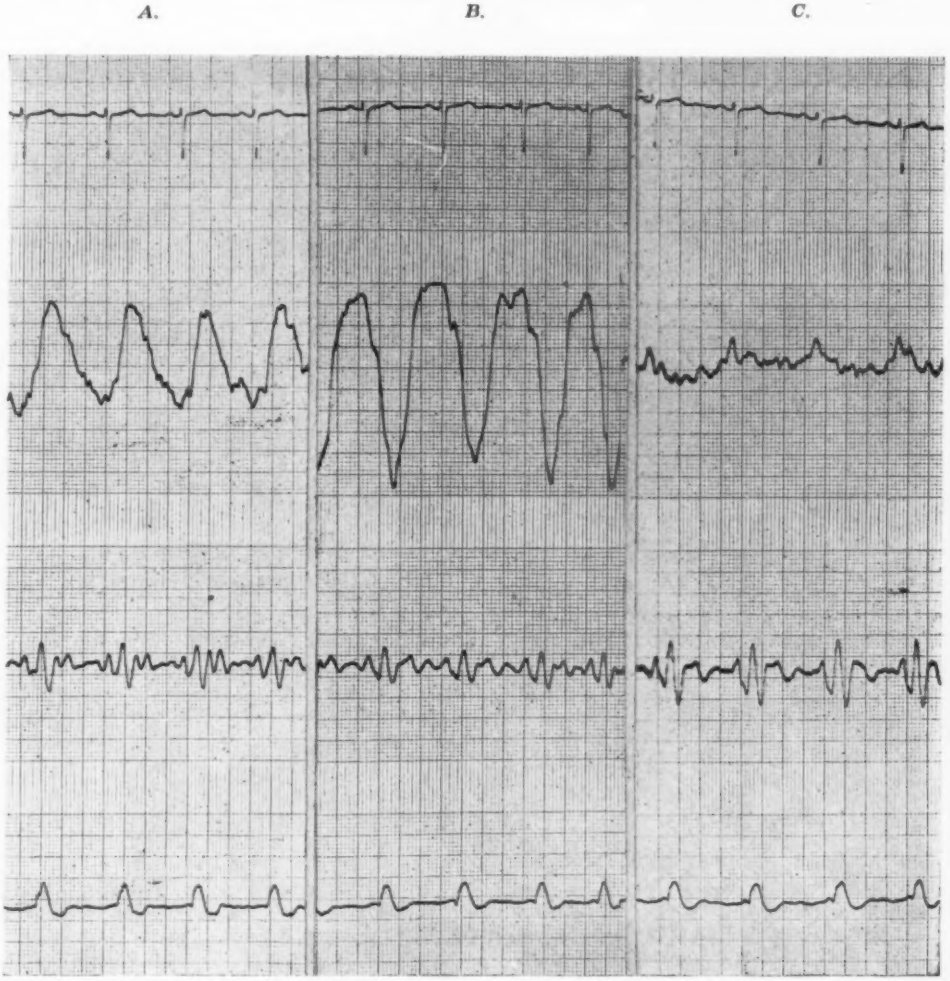

Fig. 3.—*A*, In order, from above down, are the electrocardiogram (Lead I), electrokymogram, ballistocardiogram, and femoral arterial sphygmogram, taken simultaneously on a four-channel direct-writing oscillograph. Electrokymogram (row 2) was taken with the patient in the anterior-posterior recumbent position and the slit of the pickup over the pulmonary artery at the left cardiac border. Sensitivity had to be raised to 5 units coarse and 16 fine. Except for tremor the curve is normal in onset, rise, descending limb, and incisura. Ballistocardiogram (row 3) reveals normal-sized waves of normal pattern and normal time relations. *B*, Rows 1, 3, and 4 as in *A*. The second row is the electrokymogram of the left ventricle taken with the patient in same position as *A* but with the slit of the pickup placed at the left cardiac border about the middle of the ventricular curve. The motion of this border was presumed to be that of the left ventricle. The size, shape, and timing of the curve are within the normal. *C*, Rows 1, 3, and 4 as in *A* and *B*. Row 2 is the electrokymogram of the right cardiac border, the right atrium. There is a prominent atrial pulse wave (venous "a" wave).

aneurysmal dilatation of the major pulmonary arteries, matching the proved case of Bedford and associates[1]; (4) the failure to find, after long and careful investigation, other suitable explanation for all the unusual pathologic findings; (5) schistosomiasis satisfactorily accounted for all the urinary, pulmonary, and cardiac findings and adequate exposure to such infestation had occurred.

The patient was then given a course of Fuadin injections. Several weeks after the last of a series of ten injections of Fuadin, an examination of a specimen of urine revealed the presence of several ova of Schistosoma with small terminal spines. This was confirmation of the diagnosis of schistosomiasis. After Fuadin therapy the patient did not appear to improve. Shortness of breath on mild effort and weakness continued but he was up and about. During these weeks there

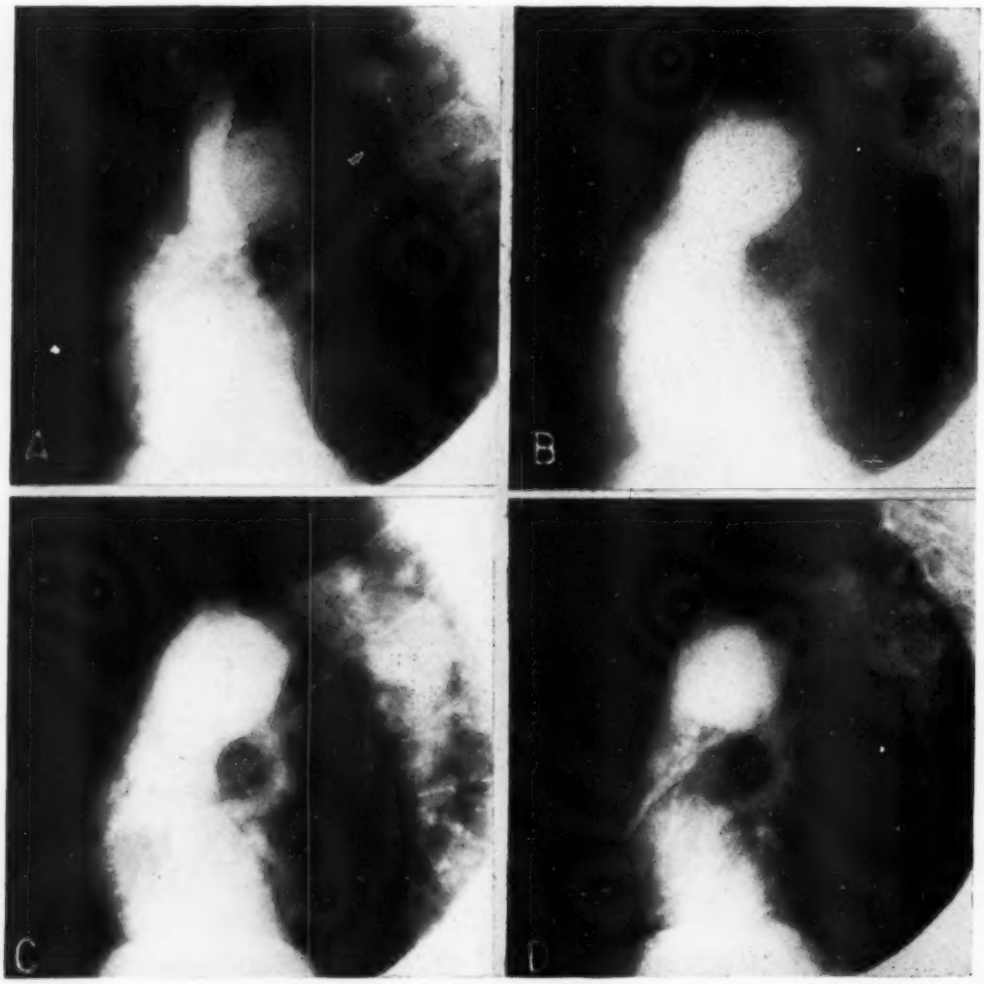

Fig. 4.—Angiocardiogram. *A*, Two seconds after injection, shows the contrast material going from the superior vena cava into the right atrium which does not appear significantly enlarged. The right auricular appendage, right ventricle, and pulmonary arteries are partly opacified. *B*, Four seconds after injection the opacification of the right atrium is less; the right ventricle, pulmonary artery, and its large left branch are more clearly visualized. *C*, Six seconds after injection opacification of the right ventricle is less but the interventricular septum clearly seen bulging convexly to the left—a reverse Bernheim sign—indicates considerable strain and some dilatation of the right ventricle. The large pulmonary artery, its large right and left branches, and more distal branches are seen, all markedly dilated. *D*, After twelve seconds the left ventricle still is not clearly opacified, the aorta very slightly so, and the right side still reveals the presence of some dye.

were no other evidences of cardiac failure. The neck veins were not unduly filled. There was no ankle edema, and râles were not heard at the lung bases. On Friday, Nov. 15, 1951, one week after the last of a second course of ten injections of Fuadin, he did not feel well enough to go to the doctor's office for his regular visit, but he did go out into the street. At about 4 P.M. he was at home and took a shower. His wife suddenly heard a loud noise in the bathroom, went in and found him in the bathtub dead. There was no water in the tub. Strenuous efforts to obtain a post-mortem examination were unsuccessful.

DISCUSSION

The history of pulmonary schistosomiasis was well recorded by Professor Erfan[2] of Egypt in his recent lecture before the Royal Society of Tropical Medicine and Hygiene in London. The ova were first observed in the lungs in 1885 by Belleli, but the clinical picture of asthma due to schistosomiasis was not reported until 1930 by Suarez.[10] The first clinical description of right-sided congestive heart failure due to pulmonary bilharzia has been attributed to Azmy Bey in 1932.[11] In Egypt the name "Azmy's disease" has been used as a synonym to bilharzial Ayerza's disease. Clarke and Graef,[12] Shaw and Ghareeb,[5] Bedford and associates,[1] and Kenawy[3] have given good descriptions of the pulmonary pathology. The lesion causing bilharzic cor pulmonale is an extensive obliterating pulmonary endarteritis due to massive and repeated infection of the lungs with ova. It was found in six out of 282 cases (2.1 per cent) in which necropsy revealed schistosomiasis, and in 6.3 per cent of the pulmonary cases by Shaw and Ghareeb.[5] Two other types of pulmonary lesions were also described by them. One was the simple perivascular parenchymal tubercle, 250 to 350 microns, developing around two or more ova. This was benign, seen in many cases but usually not numerous in any patient. The third type of pulmonary lesion was uncommon; it consisted of a focal necrotizing arteriolitis, insufficient in number to cause hypertrophy of the right heart or congestive heart failure. These lesions were found in six of their 282 cases. After recanalization and the formation of new capillaries, the vascular lesions developed a characteristic appearance which they called angiomatoid. Worms were found in the lungs in ten of their cases, or 3.6 per cent; in two of the ten they were alive, in the remainder they were dead and had caused a toxic focal pneumonia.

The definitive diagnosis of schistosomiasis is based upon the finding of the ova or worms. The demonstration of eggs, however, may not be easy or always possible. Sayegh (1950) reported a urological study of 653 patients admitted to the American Hospital in Egypt, ". . . who on repeated examinations showed no ova in the urine yet suffered from lesions caused beyond doubt by their initial bilharzial infection."[15] Sputum examinations would seem to be helpful in the diagnosis of the pulmonary form, but ova are said to be rarely found there. Alves and Blair[19] examined one pint of a patient's sputum, after concentrating it with potassium hydroxide and centrifuging the digest, to find but one terminal spined egg. In our case there was no expectoration. Ova were not found in the urine on repeated examinations of centrifuged specimens, but were finally seen on one occasion after provocative injections.[16] If ova should not be found, the diagnosis may then be made on ". . . certain conclusive or highly suggestive signs of the disease" (Gelfand).[6] He found diagnostic criteria such as the intradermal reaction and

blood eosinophilia had a useful place but were "of limited value." He found the skin test negative in thirty-four of 100 patients passing ova and positive in 20 per cent of non-bilharzial subjects. In his large experience eosinophilia was absent in 50 per cent of the cases. It was usually absent in the advanced chronic cases according to Kenawy.[3] The complement fixation test (Fairley) remains positive only as long as living worms persist in the host.[17] In a study of 600 cases of *Schistosomiasis japonicum* by Most and associates[18] the Fairley test was positive in only 23 per cent of patients with clinical evidence of the disease but without eggs in the stools. There was about the same percentage of positive patients in a control group. Lesions of the bladder were not visible to the naked eye in 30 per cent of Gelfand's autopsy series but after digestion of the bladder in caustic potash ova could be demonstrated. Snippings taken from any portion of the bladder or rectum of suspected patients, even though no gross lesions were visible, are likely to disclose ova, according to Gelfand. Snippings from the bladder were sought in our case but the patient refused to give consent for the examination. In 250 bilharzial cases Gelfand found gross lesions of the ureters in 30 per cent; 27 per cent dilatation alone, 3 per cent stenosis; 15 per cent had some hydronephrosis, and only 3 had infected calculi. In our patient the finding of blood and casts in the urine collected from ureters indicated the presence of ureteral and renal lesions as described above in addition to the bilharzic cor pulmonale.

SUMMARY AND CONCLUSION

A case of schistosomal heart disease, bilharzic cor pulmonale, is described. A presumptive diagnosis first was made on the history of adequate exposure to the cercariae, the development of hematuria within a year thereafter, and its persistence for eight years, without other known cause, the presence of the characteristic though rare cor pulmonale with aneurysmal dilatation of the major pulmonary arteries seen in the angiocardiogram, and the careful exclusion of other causes such as hemolytic disease and atrial septal defect.

A definitive diagnosis was finally established by the finding of ova of *S. haematobium* in the urine. An angiocardiogram, electrokymogram, ballistocardiogram and twelve lead electrocardiograms of this condition are reported for the first time. This is the first case reported in which an ante-mortem diagnosis of bilharzial heart disease was made in this country. Schistosomiasis may be an important and unrecognized cause of cor pulmonale among those who have been in countries where this disease is prevalent.

We wish to thank Dr. Nathan Rosenthal for having referred the patient, A.W., to us.

ADDENDUM

Since this article was submitted for publication, two papers have appeared on this subject: one from Egypt—Girgis, B.: Pulmonary Heart Disease Due to Bilharzia; the Bilharzial Cor Pulmonale, AM. HEART J. 43: 606, 1952; the other paper from Brazil: Barbato, E., Pinto Lima, F., Cotrim, E., Merlino, G., and Moraes Dantos, O.: Some Aspects of the Pulmonary Artery in Schistosomiasis Importance in the Differential Diagnosis With Congenital Heart Disease, Aro. brasil. cardiol. 4:233, 1951 (abstract: Circulation 4:630, 1952).

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NECROSIS OF A CARDIAC PAPILLARY MUSCLE FOLLOWING INFARCTION WITH INCOMPLETE RUPTURE

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COMPLETE rupture of a papillary muscle after cardiac infarction has been reported in about forty instances.[1] It is a catastrophic complication and usually results quickly in death. The differential diagnosis from septal perforation is at times difficult. The presence of a thrill in addition to a sudden developing murmur usually favors the diagnosis of septal perforation. A thrill does not occur in complete rupture of a papillary muscle.[1] This case is apparently the first reported instance of almost complete necrosis of a papillary muscle without rupture. Persistence of the muscle as fine synechial strands was associated with the presence of a thrill.

CASE REPORT

A 61-year-old spinster was first seen Dec. 1, 1947, suffering with hypertensive cardiovascular disease, coronary arterial disease, angina pectoris, and diabetes mellitus. There were no significant cardiac murmurs. The hypertension and the angina required her retirement as a teacher in February, 1949.

On Sept. 19, 1951, she developed sudden, severe, crushing pain over the lower sternum, radiating into both arms, not relieved by nitroglycerin. On Sept. 21, 1951, the systolic blood pressure, which usually averaged 200 to 230 mm. Hg dropped to 141. The severity of the pain continued. On September 25 the patient entered St. Vincent's Hospital. At this time a harsh medium-pitched systolic murmur of Grade IV intensity was heard, of maximum intensity over the apex. It had not been heard before the attack. An electrocardiogram September 26 showed intraventricular conduction defect, left axis shift, and wandering pacemaker. The leukocyte count was 18,000. The blood sugar was 315 mg. per 100 c.c. blood. The patient was in shock, the blood pressure being 40 to 60 mm. Hg, which gradually rose to 110. The pain was extremely severe. Because of shock and cyanosis, oxygen was needed continuously. The possibility of a dissecting aneurysm was considered. On September 29, however, progressive changes of the electrocardiographic pattern were considered diagnostic of myocardial infarction (Fig. 1). The condition was critical for several days. Pulmonary edema became acute at times and râles in the lungs never completely disappeared. Very slight physical or emotional disturbance elicited marked dyspnea, cyanosis, and pulmonary edema. The murmur varied somewhat in intensity, but developed a high-pitched musical quality. A thrill was felt at times over the apex. The liver became swollen and tender. Rupture of the heart was accepted as the diagnosis, but because of the thrill, perforation of the septum was favored. In all reported cases of complete rupture of a papillary muscle in no instance had a thrill ever been felt.[1] Enlargement of the liver increased; edema and anasarca gradually developed despite the use of digitalis and mercurial diuretics. The patient died Jan. 20, 1952, four months after the sudden onset of this illness.

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*Autopsy.**—On opening the pleural cavities, there were no adhesions on either side, but there were 1,500 c.c. of clear straw-colored fluid in the right chest and 1,000 c.c. in the left chest. The transverse pericardium measured 16 cm. The sac contained only 10 c.c. of clear straw-colored fluid. The heart weighed 320 grams. The right side of the heart was considerably dilated and distended with blood. The left ventricle was also dilated with an aneurysmal outpouching posterolaterally in the area of a previous infarction. The heart had almost a spherical outline

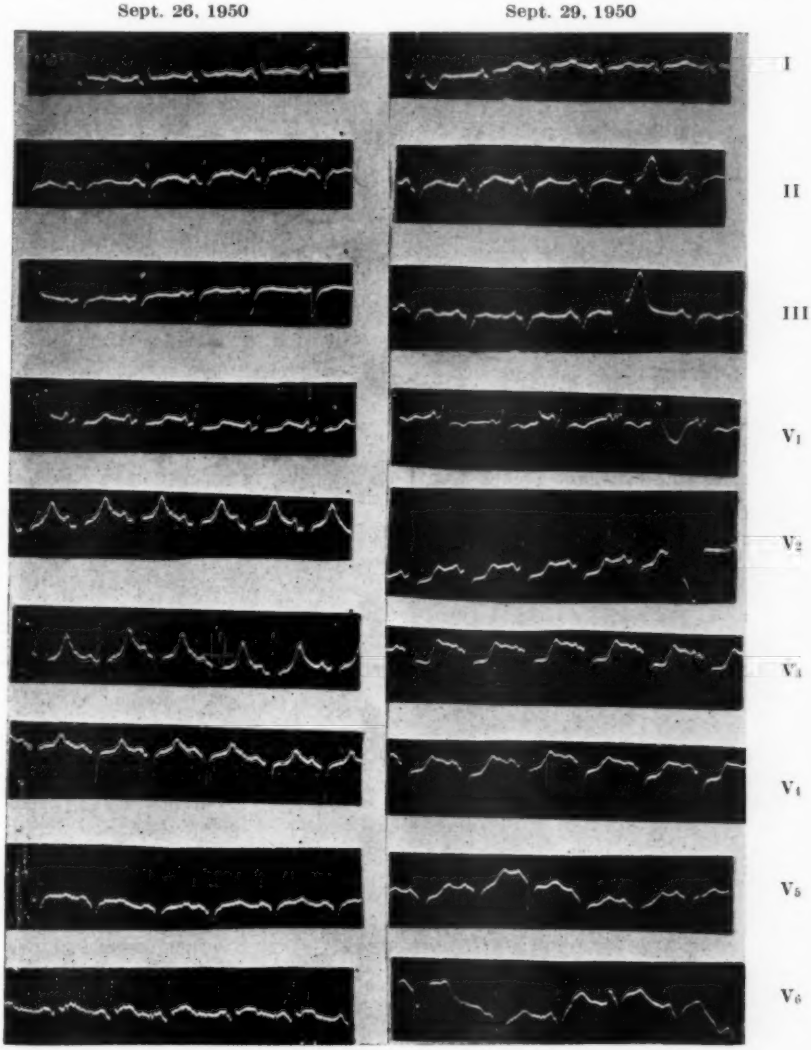

Fig. 1.

due to the bulging of the ventricles as well as the dilatation of the auricles. Posterolaterally, there was a whitish scarring showing through in the area of aneurysmal dilatation, otherwise the epicardial surface contained a normal amount of fat and no soldier spots. The coronary arteries were investigated before the heart was opened. There was Grade III sclerosis of all the coronary branches and there was an old grayish-brown thrombus occluding the left circumflex 3 cm. from its origin. There was also an area of marked diminution in the size of the lumen due to ather-

*Dr. J. M. Kahler performed the necropsy.

osclerosis without thrombosis in the left descending coronary branch about 4 cm. from its point of origin. When the heart was opened, the attention was focused on the posterior papillary muscle in the left ventricle. This muscle was represented by a pale yellow infarcted irregular mass of tissue measuring 1.7 × 1.1 × 0.3 cm. and appeared to be suspended in the center of the ventricle by the chordae tendineae on one side and by fine wisplike strands of attenuated whitish muscle toward the ventricular side. There had been infarction of the myocardium just under the area in which the muscle arose, so that there had been an almost complete rupture of the posterior papillary muscle, but it had remained attached to the myocardium by five tiny white strands (Figs. 2 and 3). These varied from 1.5 to 0.9 cm. in length. None was more than 1 mm. in width or thickness. On the other hand, the average length of the chordae tendineae was 1.7 cm.; they were also about 1 mm. in thickness. The area of infarction which underlay the base of the papillary muscle or its previous base measured 3.5 × 4 cm. On the ventricular aspect it was white and

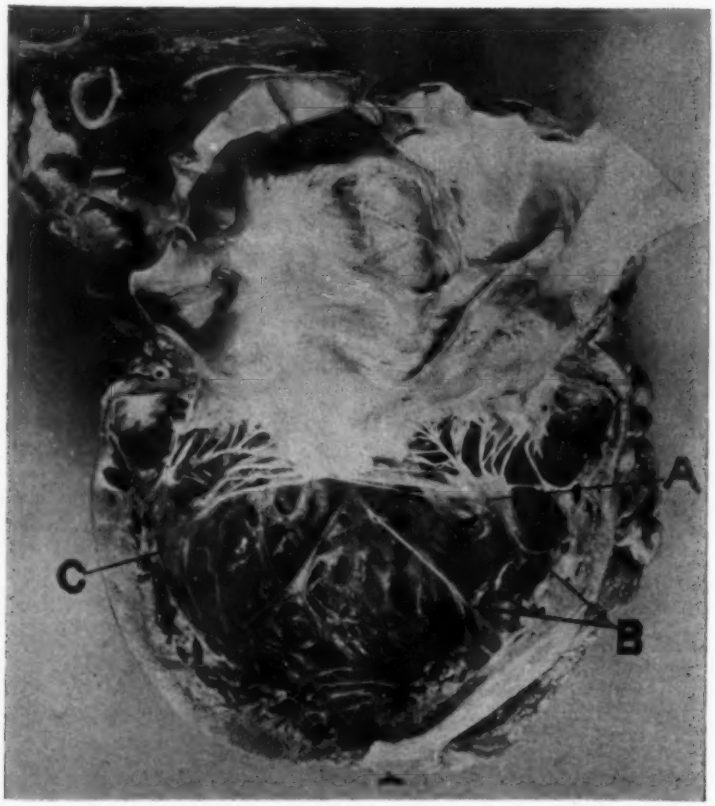

Fig. 2.—The opened left auricle and ventricle are shown. At *A* the remnant of the posterior papillary muscle can be seen attached to the ventricular muscle by the thin bands (*B*). These thin bands are all that remain of the mass of muscle which, before infarction, had the same volume as the base of attachment to the anterior papillary muscle (*C*).

smooth, but, when cut across, there was still a thin bank of muscle tissue between the scar and the epicardial fat. The infarction involved principally a portion of the deep bulbospiral muscle of which the posterior papillary muscle is a part. The infarction occurred on the posterolateral surface of the ventricle. There was no infarction of the septum or of the remainder of the myocardium. The anterior papillary muscle in comparison had a base of origin from the myocardium 2 cm. in diameter while the muscle proper measured 2 cm. in width and 7 mm. in thickness. The left ventricle was 7 cm. in thickness. The mitral valve was 9 cm. in circumference, the tricuspid 13 cm., the pulmonic 8 cm., and the aortic 7 cm. The left auricle appeared normal. The right auricle and the right ventricle were markedly dilated and there was a large thrombus in the right

auricle. The foramen ovale was patent. There was Grade III atherosclerosis throughout the aorta.

Microscopic Description.—A section of the small deformed and discolored area remaining in the posterior papillary muscle showed destruction of 25 per cent of the muscle fibers present. Only a few groups of muscle cells remained at the outside of the mass and even in these cells there was considerable breaking up of the sarcoplasm although the nuclei remained normal in appearance. The remainder of the muscle fibers had been replaced by a hyalinized pale-staining fibrous tissue which was extensively calcified and contained numerous hemosiderin macrophages.

Fig. 3.—Slight rotation of the same specimen as in Fig. 2 accentuates the shadow of the aneurysmal bulge of the infarcted muscle beneath and behind the posterior papillary muscle again labeled *A* and *B*.

There were no vessels visible in this fibrotic calcified portion. The endocardial cells overlying this muscle group were normal in appearance and there was no endocardial thrombosis. Sections of the myocardium beneath this damaged papillary muscle showed similar fibrous replacement of muscle tissue plus new tiny vessels and numerous macrophages replacing the muscle in the inner half of the thinned-out myocardial wall and with relatively normal muscle fibers in the outer half of the myocardium. Sections from elsewhere in the myocardium showed no lesion.

Anatomic Diagnoses.—Myocardial infarction due to coronary thrombosis (infarction of posterior ventricular myocardium and of posterior papillary muscle with incomplete rupture of latter).

DISCUSSION

This apparently is the first reported instance of an incomplete rupture of a papillary muscle after myocardial infarction. It was not considered as a possibility in the diagnosis because there were no previous reports to indicate that it occurred. The papillary muscle as a site of rupture was excluded because of the presence of a thrill. The mechanism of production of the thrill in this case was probably related to the action of the fine persisting strands producing eddy currents and vibrations during systole. The infarction of the papillary muscle apparently resulted from an extension of necrosis from the deep bulbospiral muscle, of which the papillary muscle is a part.

SUMMARY

A case of incomplete rupture of a papillary muscle of the left ventricle of the heart following infarction of the deep bulbospiral muscle is recorded.

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BALLISTOCARDIOGRAPHIC FINDINGS IN A CASE OF PULSUS ALTERNANS

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WE HAVE recently had the opportunity to examine a patient who presented pulsus alternans and to record his ballistocardiogram. In view of the fact that the literature (to our knowledge) does not contain an example of the ballistocardiogram of this phenomenon, it was felt the observation should be reported.

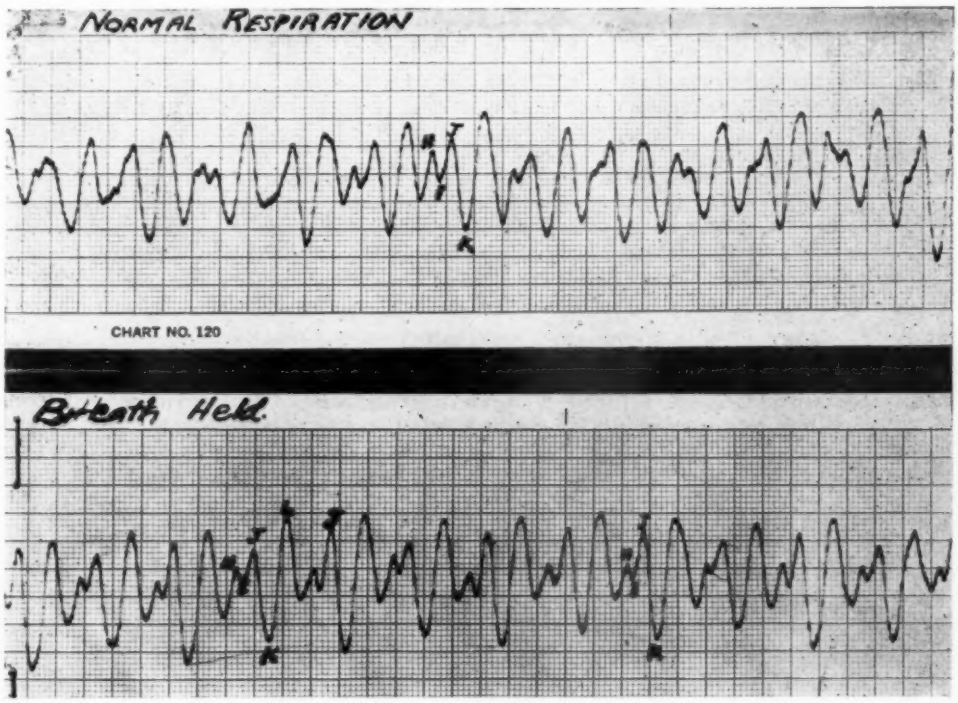

Fig. 1.

CASE REPORT

W. H., a 60-year-old white man, was examined Dec. 5, 1951. His chief complaints were progressive exertional dyspnea and weakness of two years' duration, urinary frequency, and nocturia. Hypertension was first found three years previously.

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The heart was found to be grossly enlarged on percussion and x-ray examination. The heart sounds were normal except for accentuation of A_2. Physical examination and x-ray examination of the lungs were normal. The liver was slightly enlarged on palpation. There was no peripheral edema.

Pulsus alternans was found when taking the blood pressure by the auscultatory method. Alternation was present between 250 and 215 mm. Hg systolic, with the diastolic at 160 mm. Hg.

The electrocardiogram showed sinus rhythm at a rate of 110 with depression of S-T in Leads I and II and a negative T_1. The descending limb of R_2 was slurred. The apex of R_3 was deeply notched. One ventricular premature systole was noted in Lead III. S-T was markedly depressed and T negative from V_4 through V_6.

The ballistocardiogram (Fig. 1) taken with the Dock two-coil electromagnetic apparatus shows an abnormal resting tracing. A tracing was then recorded, with the patient holding the breath, to observe the effect of removing the respiratory variation. This strip clearly shows alternation in the height of IJ waves. The length of JK also showed a similar variation.

It is interesting to note that alternation of the pulse was brought out in this case when the breath was held and the usual respiratory changes of the ballistocardiogram had been eliminated. It is therefore recommended that tracings be taken both during normal respiration and breath holding. It is of further interest that in cases of marked tachypnea in which a 2:1 pulse-respiration relationship exists, pseudo-alternation may occur due to the effect of breathing on the peripheral pulse. Breath holding in this instance will eliminate the phenomenon. In our patient true alternans was brought out ballistocardiographically by breath holding.

The exact mechanism of pulsus alternans is not well understood, although it is believed to be due to the inability of the ventricular muscle to contract as a whole to each stimulus. Ballistocardiography may provide a new tool for the ready study of that disturbance. The genesis of the component waves of the ballistocardiogram is thought to be fairly well known. Observations of various circulatory phenomena, such as pulsus alternans, may, conceivably, throw additional light on ballistic theory.

BOECK'S SARCOID WITH UNUSUAL CARDIAC CONFIGURATION AND ELECTROCARDIOGRAPHIC CHANGES

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NEW YORK, N. Y.

SARCOIDOSIS is a generalized disease that may involve any organ of the body. Hutchinson[1] first described sarcoid as a disease of the skin in 1875. Since then, sarcoid has been looked upon as a generalized granulomatous process affecting many organs including the heart.[2-9] Occasionally, the myocardial involvement is responsible for the presenting clinical symptoms. However, in most cases, the lesions are incidental autopsy findings and clinically unimportant.

The case to be described is primarily one of pulmonary and mediastinal sarcoidosis with unusual cardiac configuration and electrocardiographic changes.

CASE REPORT

A. S., a 30-year-old white man, was admitted on March 15, 1951, with the chief complaints of malaise, fever, and sweats of four months' duration. A vaguely-remembered illness was diagnosed as "rheumatic fever" at 18 years of age. Nine years ago, the patient was rejected for military service because of a "heart condition." Since then, he had been well except for the onset of dyspnea on exertion two years before admission.

The present illness began three weeks before admission with the gradual onset of malaise, fever, aching joints, sweats, anorexia, and weight loss. The dyspnea became worse and was aggravated by the fever. A dry cough was troublesome but there was no hemoptysis. He was treated for "rheumatic heart disease and congestive failure" with digitalis and a salt-free diet. Because of continued fever and lack of improvement, he was admitted by the referring physician with a diagnosis of "acute exacerbation of rheumatic fever."

Physical examination revealed the patient to be a thin, chronically ill, white man with mild dyspnea. He complained of a "feeling of pressure" substernally and coughed frequently to clear this "pressure," without producing any sputum. The neck veins were not distended. There was no significant adenopathy except for a node, the size of a large pea, in the right supraclavicular region. The chest was markedly emphysematous. The lungs were clear. There were no thrills. The point of maximum impulse was displaced just to the left of the xiphoid process in the sixth intercostal space. The heart sounds were loudest there. The first sound was loud and snapping and was followed by a Grade II, slightly harsh, blowing systolic murmur. The second sound was reduplicated. A short indistinct, harsh adventitious sound was occasionally heard in mid-diastole. P_4 was greater than A_2. There was regular sinus rhythm with occasional atrial premature contractions. The ventricular and pulse rates were 96 per minute. The blood pressure was 130 mm. Hg systolic and 84 mm. Hg diastolic. The liver and spleen were not felt.

From the Departments of Medicine and Cardiovascular Research, The Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, N. Y.
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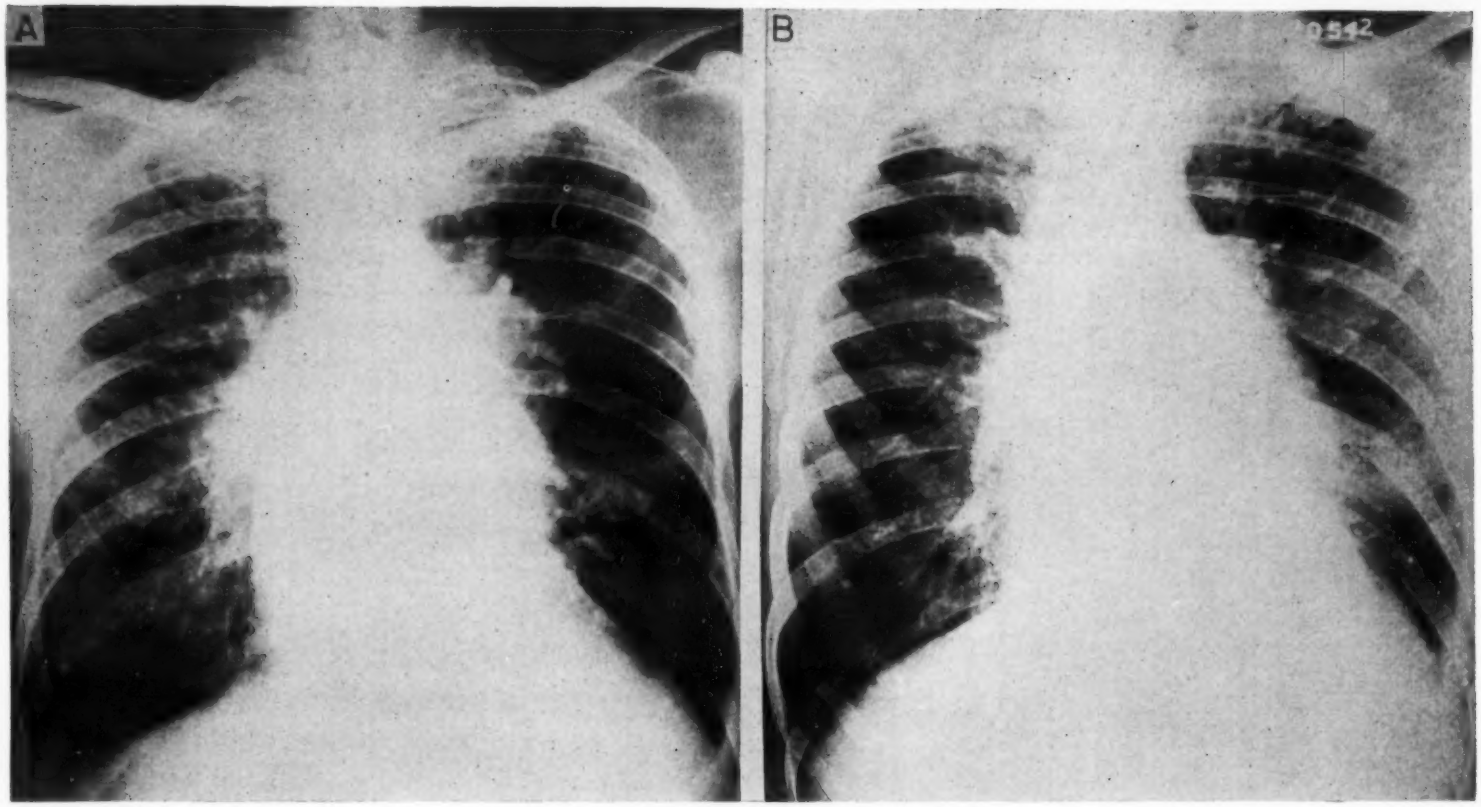
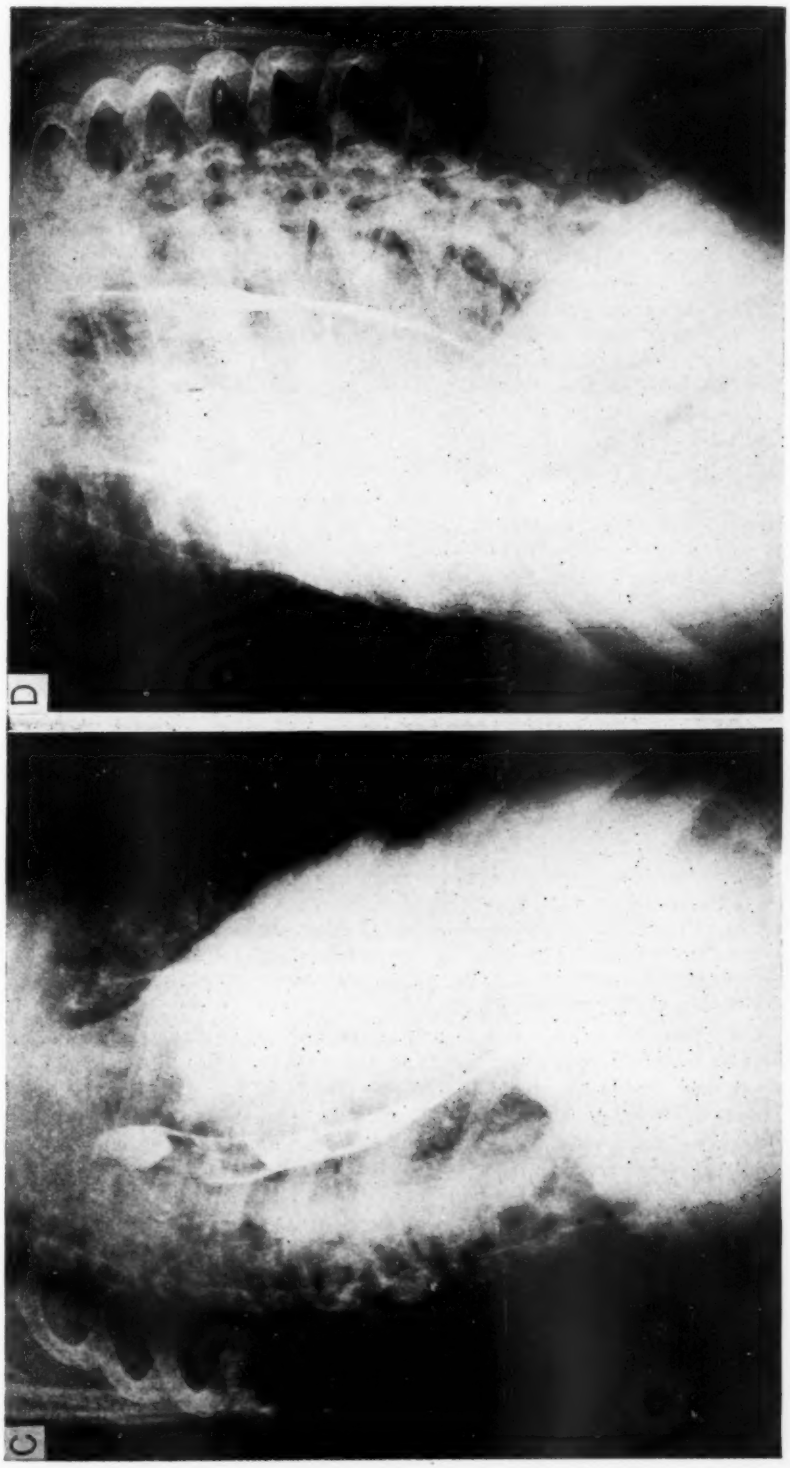


A. *B.*

Fig. 1.—*A*, Posteroanterior view. The cardiac configuration is globular and elongated as if the heart were rotated into the left oblique view. The pulmonary infiltrate and hilar masses are evident. *B*, Partial right oblique view. The cardiac configuration is now like that usually seen in the posteroanterior view.



D.

C.

Fig. 1.—*C*, Right oblique view. The barium-filled esophagus is not displaced. There is no chamber enlargement. *D*, Left oblique view. There is no chamber enlargement.

Laboratory Findings.—The hemoglobin varied between 13.0 and 14.0 Gm. per 100 c.c. of blood. The red cell count varied between 4.66 and 5.71 million per c.mm. of blood. A representative differential count before radiotherapy was instituted revealed 60 per cent polymorphonuclear leukocytes, 13 per cent band forms, 20 per cent lymphocytes, 4 per cent monocytes, and 3 per cent eosinophils. During radiotherapy, the eosinophil count increased from 8 to 22 per cent. Bone marrow aspiration revealed slight erythrogenesis and a slight shift to the left of the granulocytic elements. Urinalysis showed a trace of albumin, good concentration to 1.030, and a negative microscopic examination. The corrected sedimentation rate varied from 15 to 38 mm. (Wintrobe). There was no growth in two blood cultures. Examination of the stool for blood, ova, parasites, and pathogenic organisms was negative. Chemical determinations of the blood were all within normal limits except for abnormalities in the blood proteins. The total protein was 7.3 Gm. per cent. The electrophoretic pattern showed a decreased albumin of 3.2 Gm., an increased globulin of 4.1 Gm., and an increased gamma globulin of 2.0 Gm. per cent. The thymol turbidity of 2.5 units was normal. The cephalin flocculation was 3 plus, and the zinc turbidity was borderline at 13.0 units. The total cholesterol was 178 mg. per cent with 88 per cent esters. Examination of the sputum was negative for tubercle bacilli. The tuberculin test was negative to 0.005 mg. of purified protein.

X-ray and Fluoroscopic Examination (Figs. 1,A and B, and 1,C and D).—The heart was not grossly enlarged. The shape was peculiarly globular and elongated and resembled somewhat the cardiac configuration as it is seen in the left oblique view (Fig. 1,*A*). The cardiac configuration was that usually seen in the posteroanterior view when the patient was rotated into a slight right oblique position (Fig. 1,*B*). There was a mass of nodes in the region of the pulmonary artery segment. There was a triangular adhesion just above this region. The pulmonary artery to the left lower lobe, visible because of the cardiac rotation, was not enlarged. The main pulmonary artery was not seen. There was no displacement of the barium-filled esophagus in the posteroanterior or oblique views. There was no evidence of chamber enlargement in the oblique views (Fig. 1,*C* and *D*).

Routine chest films, Bucky and laminographic studies revealed a diffuse, generalized infiltration throughout both lungs, most marked in the upper lobes. The domes of the diaphragm were elevated and adhered mesially to the pericardium. Considerable emphysema was present. There was marked adenopathy at both hili.

Electrocardiogram (Figs. 2 to 4).—The electrocardiogram showed regular sinus rhythm, rate 107 per minute, with occasional ventricular premature contractions (Fig. 2). Right axis deviation was present. P_2 and P_3 were broad and prominent. A terminal r was seen in aV_R and the T wave was flat in aV_L. Circumferential chest leads failed to detect a predominantly tall R, although R was greater than S in V_6, V_7, and V_8. A predominantly tall R was recorded over the left upper quadrant and over the precordium at the level of the sixth intercostal space in positions corresponding to V_4, V_5, V_6, V_7, and V_8 (Fig. 3).

In the esophageal leads (Fig. 4), where E_1 was at the diaphragm, a tall R preceded by a q was recorded for a distance of 5.3 cm. above the diaphragm. The P waves were prominent in the esophageal leads as they were in the precordial and standard leads.

Course.—It became evident quite early in the hospital stay that the patient was not in congestive failure. This was substantiated by a normal veuous pressure of 11.5 cm. of water with no rise on right upper quadrant pressure. The ether circulation time was 9.0 seconds, and Decholin time was 18 seconds. The fluoroscopic and radiographic findings strongly suggested the diagnosis of Boeck's sarcoid of the lung. The small node in the right supraclavicular area was biopsied. Microscopic examinatlon showed a lymph gland containing small and large discrete tubercle-like granulomas which consisted of epitheloid cells, occasional multinucleated giant cells, and very few lymphocytes. The intervening lymphatic tissue was hyperplastic. The diagnosis was Boeck's sarcoid.

The patient's course was complicated by diarrhea. Radiographic examination of the entire gastrointestinal tract failed to show evidence of sarcoid. A small pedunculated anal mass was found by proctoscopic examination. The morphology was typical of a polyp covered with squamous epithelium. No sarcoid granulomas were present. The diarrhea stopped with the removal of the polyp.

Further search for sarcoid lesions was made but none were found. The fundi were normal. A complete survey of the bony skeleton failed to reveal sarcoid.

Radiotherapy was given to the lungs and mediastinum from April 26, 1951, to July 30, 1951, in a total dosage of 3,250 r. The vital capacity which was 2,700 c.c. increased to 3,600 c.c. However, there was no change in the roentgenologic appearance of the lungs.

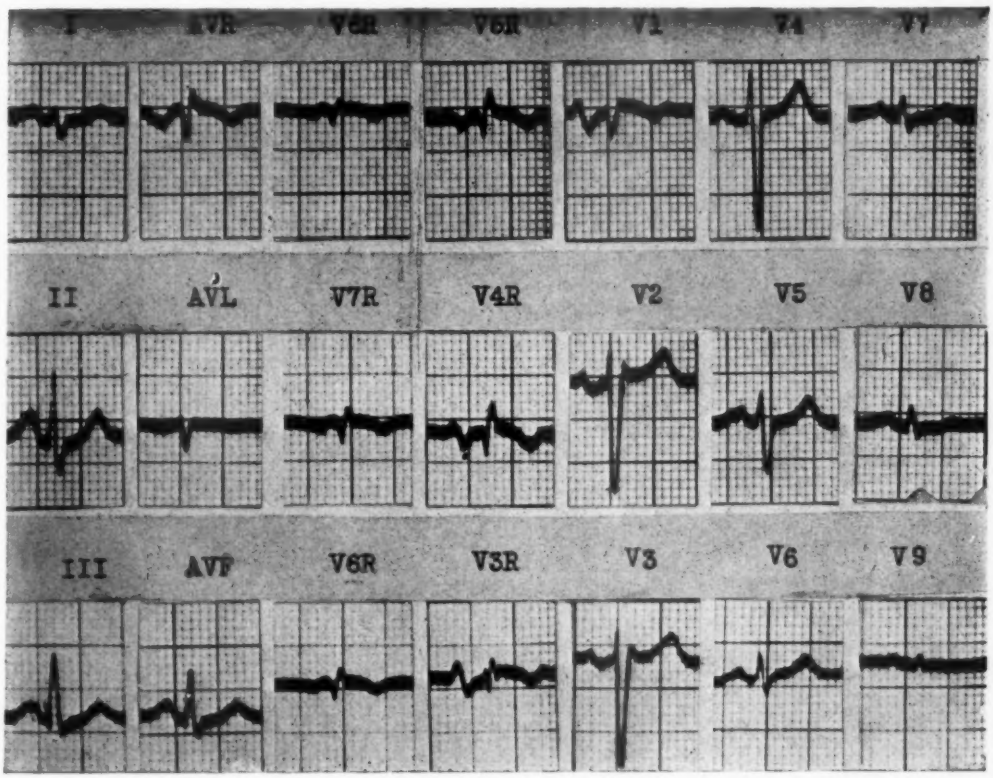


Fig. 2.—The electrocardiogram shows right axis deviation and prominent P waves. Predominant positivity (tall R) is not seen in the circumferential precordial leads. (V_R are leads from the right precordium taken at the level of the fifth intercostal space. The three leads in vertical alignment were taken simultaneously with the Technicon Tri-Beam.)

COMMENT

The diagnosis of rheumatic heart disease with activity was doubtful from the very first physical examination and fluoroscopy. Although the first heart sound at the apex was loud and snapping, the characteristic murmur of mitral stenosis was absent. The blowing systolic murmur was localized at the displaced point of maximum impulse. The cardiac configuration was also not that seen in rheumatic heart disease. There was no left atrial enlargement and no prominence of the pulmonary artery segment. The size was normal, but the shape was peculiarly elongated and globular as if the heart were rotated into a left oblique position. The lungs were obviously diffusely involved by an infiltrative, fibrotic process, with hilar adenopathy and pleuropericardial adhesions. Dyspnea and cough were considered secondary to the pulmonary involvement.

The electrocardiographic changes could have resulted from either right atrial and right ventricular hypertrophy, or from rotation per se. The predominant positivity (tall R wave) in the precordial leads was displaced downward and to the left. In the presence of anatomic rotation and displacement of the heart and the shift of the predominant positivity (tall R), the electrocardiographic changes most probably resulted from a rotation of the electrical axis in space, independent of atrial and ventricular hypertrophy.

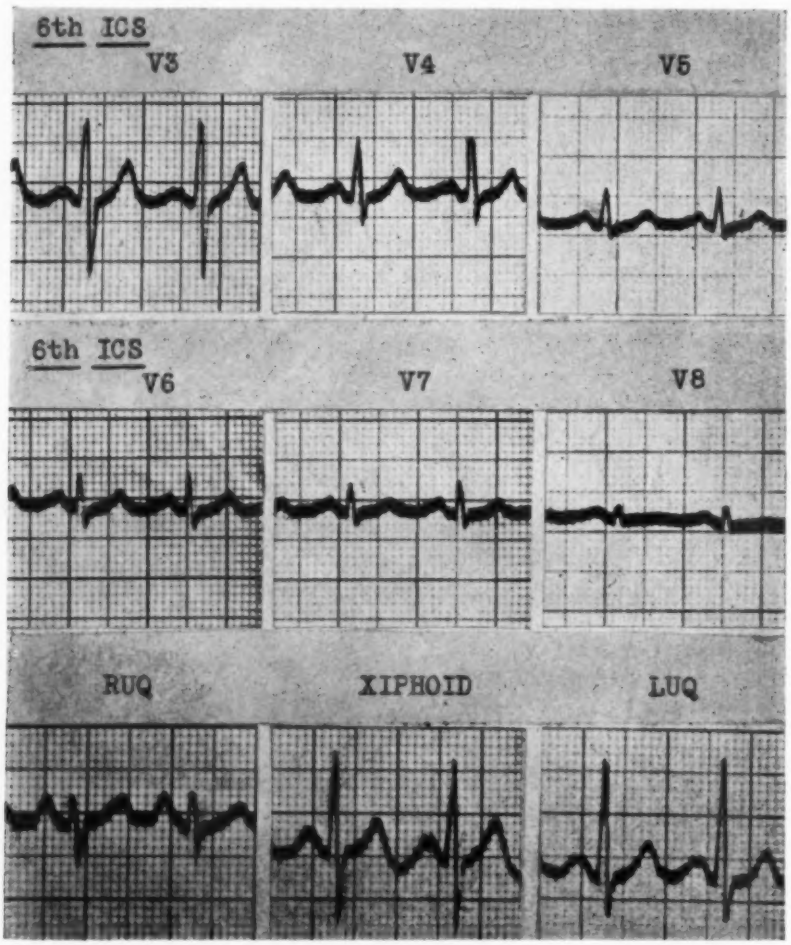


Fig. 3.—Predominant positivity (tall R) has been displaced to the left precordium at the level of the sixth intercostal space and downward to the left upper quadrant.

DISCUSSION

Sarcoidosis may involve any portion of the heart and yet produce no clinical symptoms.[10-13]

Sarcoid may involve the heart primarily and produce disturbances in rhythm as well as heart failure. Cotter's case[14] of extensive sarcoidosis of the heart showed congestive failure, shifting pacemaker, and auricular fibrillation. Arrhythmias

were present in Salvesen's two cases.[15] In one of Longcope's cases,[8] a septal lesion accounted for heart block. Johnson and Jason's case[16] was characterized by severe heart failure with multifocal ventricular premature contractions and paroxysmal ventricular tachycardia.

Most cases of sarcoidosis of the heart fall into the group where the disturbances are secondary to pulmonary hypertension with cor pulmonale.[17-19]

Our case, however, is unique in that an abnormal unusual anatomic rotation of the heart has occurred. The electrocardiographic changes also reflect this rotation, so that the predominant positivity (tall R) is displaced from the levels at which it is normally recorded in the precordial and esophageal leads. Although some degree of right ventricular and right atrial enlargement may be present, the findings in this case are not characteristic of cor pulmonale. The anatomic and electrocardiographic rotation probably results from primary and secondary displacements—primary, by the mediastinal fibrous adhesion, and secondary, by pulmonary emphysema with unequal lung volumes.[20]

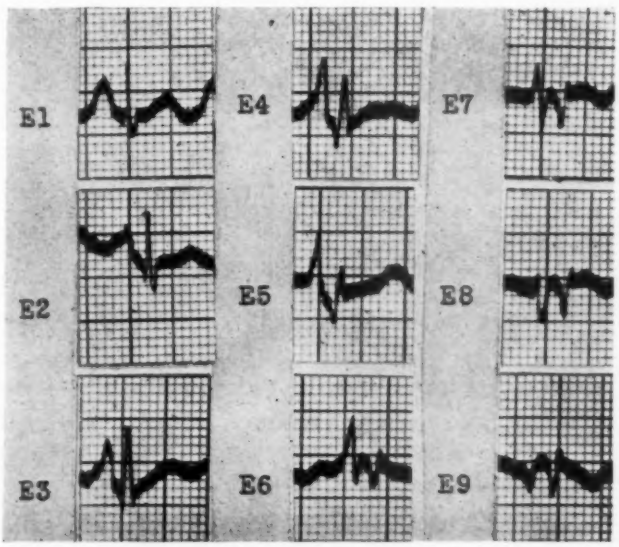


Fig. 4.—Predominant positivity (tall R) is recorded at the lower esophagus for a distance of 5.3 cm. above the diaphragm. (E_1 is at the diaphragm; the distance between leads is 1.75 cm.)

SUMMARY

1. A case of Boeck's sarcoid with unusual cardiac configuration and electrocardiographic changes is presented.

2. A review of the literature indicates that primary cardiac involvement by sarcoid may or may not produce symptoms. Occasionally, however, cardiac symptoms constitute the presenting clinical picture.

3. The most frequent secondary cardiac manifestation of sarcoidosis is cor pulmonale caused by pulmonary fibrosis and hypertension.

4. The anatomic and electrical rotation of the heart in this case is considered a rare secondary manifestation of sarcoid caused by pulmonary fibrosis and emphysema, and mediastino-pleuro-pericardial adhesions.

We want to express our appreciation to Dr. S. R. Slater, Director of Cardiovascular Research, and Dr. A. Marel for their encouragement. The photography was done by Mr. Herbert Fischler.

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Book Reviews

THE CLINICAL USE OF FLUID AND ELECTROLYTE. By John H. Bland, M.D., Philadelphia, 1952, W. B. Saunders Company, 259 pages. Price $6.50.

This 259-page monograph is an excellent presentation of the principles of fluid and electrolyte therapy in a wide variety of clinical conditions and diseases.

The first portion of the book deals with basic physiologic considerations of body fluid and electrolyte and the remaining chapters deal with correction of imbalances in various medical and surgical conditions.

In his preface Dr. Bland includes the following statements: "Awareness of departure from electrolyte and fluid normality, plus recognition of clinical symptoms and signs, as well as the proper use of repair solutions will probably be responsible for more lives saved than any other single therapeutic technique in the future. Researchers have brought electrolyte and fluid balance information to a degree of development now compatible with its use as prophylaxis." This is not an overstatement, and should be considered seriously by all clinicians, whether they be physicians or surgeons.

The material presented in this monograph is supplemented by simple diagrams, similar to those of J. L. Gamble, in which are portrayed the actual, or probable, chemical anatomy of blood plasma, interstitial fluid, and cell fluid in many different types of fluid and electrolyte imbalance. Emphasis is repeatedly placed upon the need to consider and treat each clinical problem individually. The information presented is supported by a list of key references with full titles at the end of each chapter.

Certain of the diagrams depicting the chemical anatomy of repair solutions show concentration figures slightly different from the figures used by other authors, but this does not seriously reduce the value of the diagrams as the reader may calculate and substitute his own figures.

It is felt that this is a most valuable and timely monograph concerning body fluids and electrolytes in which the author skillfully integrates information derived from both laboratory and clinical sources.

J.R.M.

CONTROL HIGH BLOOD PRESSURE AND LIVE LONGER. By Herman Pomeranz, M.D., Visiting Physician, Manhattan General Hospital, New York, N. Y., 1952, Eton Books, Inc., 239 pages. Price 35c.

This small paper-bound volume contains the available knowledge on the blood pressure, its disturbances, and the treatment of hypertension, related in such a manner that it is readily available to the lay reader. It also contains much information on the dietary treatment of hypertension, obesity, and diabetes. This book is well written, the information which it contains is accurate and unbiased excepting the fact that it emphasizes the more hopeful aspects of the disorder. Its various points are emphasized by simple, often pictographic illustrations. It appears to be as good a book as could be produced for its purpose.

The reason for reviewing it in this journal is presumably to determine whether such a book can be recommended by the physician to his patient and other lay persons who seek information on the subject. We are living in an age in which medical progress is swift and dramatic and in which a considerable portion of the lay public desires and eagerly devours information on medical matters. It is up to the medical profession to see that this desire is satisfied. There is, however, among the medical men with whom I am acquainted a widespread opinion that much of this dissemination of medical knowledge is harmful. However well presented, it often causes mental indigestion, it is often read by introspective persons and, judging from the inquiries that come to our offices as a result of these publications, they must cause a great deal of wanton and unbalanced speculation and frequently fear and worry, even when they are well written.

While I emphatically champion candor and honesty in physician-patient relationship, it does appear to me that the problem of how much a given patient should know about his condition and how that knowledge should be presented to him is one of the fine points of the practice of medicine which cannot be replaced by routine publications.

The real value of a book such as the present volume must be determined practically after it has been placed in the hands of carefully selected patients.

J.J.

DISORDERS OF THE HEART AND CIRCULATION. By Robert Levy, M.D. (Ed.) (Nelson Medical Book), Baltimore, 1951, Williams & Wilkins Company, 944 pages. Price $12.00.

This book is printed on excellent paper and has unusually clear print. It consists of a series of monographs by various authors, rather than a highly integrated textbook. The authors have been carefully selected and most of the chapters are good. It is a book which everyone with a special interest in cardiology will want to read. However, physicians with more general interests may have some difficulty in locating pertinent material, as it may be found in any one of several chapters and be omitted from chapters where one might expect to find it. The index is excellent and should help overcome this problem. It is more difficult for the student who wishes to get a complete concept of a subject in one area. In contradistinction to this, there is also considerable overlapping in some areas as in the chapters, Coronary Heart Disease, Coronary Insufficiency, and Surgical Treatment of Angina Pectoris. Each author expresses his own opinion and no attempt is made to reconcile differences. This may confuse the student but the varied concepts so forcefully presented will be enjoyed by the experienced and critical cardiologist.

An unusually long and detailed presentation on prevalence of heart disease will be of value to those working in organizations which have to present the problem to laymen.

The chapter on pericardial disease is well written and unusually complete. Too little is said about "acute nonspecific pericarditis," which is of great importance in the differential diagnosis of myocardial infarction.

The chapter on congenital heart disease is not of much practical value and was left in, as the author says, for sentimental reasons. This is more than compensated for by Bing's excellent presentation in the next chapter.

The discussion of rheumatic fever is good, but there are some omissions. The selection of cases for treatment with radioactive iodine needs attention; there should also be a critical analysis of the value of ACTH and cortisone, on the length of time for bed rest and the criteria for getting up, and finally, on sulfadiazine and penicillin prophylaxis.

Acute bacterial endocarditis and subacute bacterial endocarditis are not separated sufficiently. The section on treatment of the latter is quite good.

The chapter on management of hypertension (general management) is good.

Management of Myocardial Infarction is an excellent chapter, especially the practical advice to the patient with a healed infarct. This author is inclined to agree with the opinion on bed rest in patients with myocardial infarction expressed by Dr. Levy.

The chapter on physiology is well done by an outstanding authority. One would like to see this expanded.

Too little space is devoted to peripheral vascular disease. This should either be eliminated or increased.

A section on the differential diagnosis of chest pain by Harrison would be valuable.

Harrison's section on heart failure presents primarily one concept rather than comparing both concepts of pathogenesis.

A. J. M.

SPATIAL VECTORCARDIOGRAPHY. By A. Grishman, M.D., and L. Scherlis, M.D. Philadelphia and London, 1952, W. B. Saunders Company, 217 pages. Price $6.00.

The fundamental electrophysiologic principles and the technique of derivation are clearly and concisely treated by the authors in the early chapters of the book.

The study of the process of ventricular activation which is so important for vectorcardiographic interpretation is only superficially analyzed.

The authors insist that the "Unipolar thoracic, esophageal and intracardiac leads are conventionally regarded as recording the electrical activity of the local muscle area subjacent to them. This may be referred to as 'the concept of localized potentials.' "

No one has made such an affirmative statement, and in this respect it is important to emphasize that the tracings on unipolar leads have been referred to the potential variations of a determined zone of the heart and not only to the electrical activity on the same zone. The reason why there are not important changes in the tracings, as the exploring electrode is removed from the epicardial surface in a perpendicular line to the same surface, is explained by the fact that the axis lead does not change. In the electrocardiographic interpretation it is absolutely correct and advantageous to state, for example, that the potential variations in V_F are very similar to those that occur in some portions of the diaphragmatic aspect of the heart. When using the term "potential variations" the intrinsic and extrinsic phenomena are included. Obviously, it is indispensable to know the potential variations of the surface of the heart in normal and pathologic conditions, such as the bundle branch blocks and the ventricular hypertrophies; in this sense, recent progress has been made and great advances accomplished.

On the other hand, in animal experimentation using unipolar leads simultaneously with bipolar leads with contiguous electrodes, we can differentiate intrinsic from extrinsic phenomena (contrary to the authors' affirmation).

In accordance with the above-expressed opinion, the advantages obtained over the vectorcardiographic curves are numerous, and in this sense it is worth while to remember the statement made by Lepeschkin: "But even if faithful representation by the stereovectorcardiogram were possible, it still would furnish no information as to the parts of the heart responsible for each component of the vector loops. This can only be obtained by means of differential and unipolar epicardial, precordial, esophageal and intracardiac leads."

It is evident that the authors exaggerate, probably for the purpose of emphasizing the importance of the method on which they have worked so long and so hard, when they state: "Spatial vectorcardiography thus furnishes information over and above that which can be obtained from routine scalar electrocardiography whether interpreted in the usual manner or by vector principles."

The fact is, in my studied opinion, that the value of the method depends on the high degree of knowledge of electrocardiography possessed by the workers as compared with their experience and knowledge of vectorcardiography.

I wish to call attention to the fact that the majority of the tracings interpreted as left ventricular hypertrophy really correspond to incomplete left bundle branch block (Figs. VIII,1; VIII,2; VIII,3; VIII,5). In tracings very similar to those shown by the authors, with QRS duration less than 0.10 second, we have found initial positivity inside the left ventricular cavity of the human heart. The authors in their book completely ignore incomplete bundle branch block. In dogs we have been able to obtain about thirty transitional complexes between normal tracings and complete bundle branch block. These transitions correspond to incomplete bundle branch block. In human beings we have seen five or six of these transitional complexes. At the present, we know more about the mechanism of the incomplete and complete bundle branch block, and with this knowledge it is evident that the sense of the vectorcardiographic curve on the horizontal plane must be different in either case. Furthermore, in the majority of cases with incomplete left bundle branch block in which there is an absence of pass (jump) of the activation wave from one ventricle to the other, the activation wave arrives late to the ventricular mass, but the speed of the same wave of activation is not changed. For this reason the vectorcardiogram will not reveal conduction delays.

The criteria followed by the authors to consider those patterns with rSR′ in V_1 as characteristic of right ventricular hypertrophy when there is congenital heart disease is entirely arbitrary. The criteria followed to differentiate left ventricular hypertrophy from left bundle branch block is better, but, by all means, it has many limitations, since the exploring electrode in the esophageal leads records a mixture of potential variations derived from the left auricle and from the superior portion of the posterior aspect of the left ventricle. In addition, many of the tracings in the esophageal leads of their cases given as characteristic of left ventricular hypertrophy are very suggestive of incomplete left bundle branch block.

Also, the majority of the tracings interpreted by the authors as right ventricular hypertrophy really correspond to incomplete right bundle branch block (Figs. IX,5; IX,6; IX,8; IX,14, etc.).

In general, we can make the same considerations as we did for incomplete left bundle branch block. For example, in Fig. IX,24, there is in V_1 a complex of the rsRS type. Exactly the same type of complex is recorded in the trabecular zone and inside the right ventricular cavity of the human heart in cases of right bundle branch block.

There is in the usual electrocardiographic interpretation several empirical means to diagnose left ventricular hypertrophy in the presence of complete or incomplete left bundle branch block. Similarly, there are empirical means to diagnose right ventricular hypertrophy in the presence of complete or incomplete right bundle branch block. Nevertheless, the electrocardiographic pattern depends mainly on the conduction disorder, and not on the hypertrophy.

In addition, we do not know the influence of the position on the electrocardiographic and vectorcardiographic curves in cases of bundle branch block. Also, we do not know the influence of the ratio of the septal mass belonging to either ventricle in the morphology of bundle branch block.

The chapters dedicated to analyze the vectorcardiogram in myocardial infarction are good and certainly will help very much to the understanding of the morphology of the tracings in these lesions. Even so, in many cases there is overlooked the extension of the infarction to the septum, as this is a frequent association with incomplete left bundle branch block.

D.S.P.

HANDBOOK OF CARDIOLOGY FOR NURSES. By Dr. Walter Modell. New York, 1952, Springer Publishing Co., Inc., 356 pages. Price $3.50.

This book on heart disease is written specifically for nurses by a doctor who has been teaching nurses for many years. The field of cardiology has been presented clearly and in the traditional manner, beginning with anatomy, physiology, and pathology as background and continuing with complete cardiac examination, the course of heart disease, and the most common forms of treatment.

The cardiac examination, signs and symptoms, roentgenograms, and electrocardiography are all included by Dr. Modell. The different forms of heart disease are presented in a clear and comprehensive manner from the diagnostic and therapeutic point of view. Two very good chapters are "Complications of Heart Disease" and "Emergencies in Heart Disease." The chapter on emergencies includes what the nurse should do, particularly until the arrival of the doctor, and outlines clearly what her responsibilities may be in cardiac emergency.

The first chapter in the section dealing with the treatment of heart disease discusses general nursing care, including diet. However, not enough emphasis is placed upon the nursing care of the cardiac patient in the home or of the cardiac child who, in many instances, presents problems of great challenge to the nurse, both in hospitals and in the home. I do not feel that the nursing problems in relation to the elderly cardiac patient who is usually in the home after the acute attack has been adequately dealt with. A very good addition to this chapter on nursing care is the appendix which includes the diets most frequently used for the cardiac patient.

The chapter on nursing care might have been greatly strengthened if it had been more fully developed by a nurse experienced in this field.

Other chapters in the section on treatment of heart disease include drugs, surgery, climatotherapy, habits and hygiene, and psychotherapy. The chapter on surgery would probably have been improved if greater detail had been brought in by a surgeon and nurse, covering preoperative, operative, and postoperative treatment and nursing care.

One weak part of the book for the nurse is that the social aspects of cardiology have not been emphasized; neither have community resources with which the nurse works, particularly in the public health field, been included. An inclusion of this material in subsequent editions would make the book still more valuable to the professional nurse; also the addition of reference material would have been valuable.

This is the first book written especially for nurses in this highly specialized field of medicine and should be a real contribution, not only to nurses but to other health workers, such as the medical social worker, occupational therapist, and the rehabilitation worker.

D. N. J.